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**Long-term effects of insulin initiation in people with Type 2
Diabetes: observational and intervention studies on disease
management and patient involvement**

Ruth Mast

The study presented in this thesis was conducted at the EMGO+ Institute for Health and Care Research (www.emgo.nl) and the Department of Clinical Pharmacology and Pharmacy, VU University Medical Center, Amsterdam, The Netherlands. The EMGO+ Institute participates in the Netherlands School of Primary Care Research (CaRe) which was re-acknowledged in 2005 by the Royal Netherlands Academy of Arts and Sciences (KNAW).

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Maria Ruth Mast

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promotor: prof.dr. M.G.A.A.M. Nijpels

copromotoren: dr. J.G. Hugtenburg
dr. A.P.D. Jansen
dr. F. Rutters

Voor papa en mama

TABLE OF CONTENTS

| | | |
|-------------------|---|-----|
| Chapter 1 | General introduction | 9 |
| Chapter 2 | Time to insulin initiation and long term effects of initiating insulin in people with Type 2 Diabetes: the Hoorn Diabetes Care System Cohort Study. | 23 |
| Chapter 3 | Effectiveness of insulin therapy in people with Type 2 Diabetes in the Hoorn Diabetes Care System: an observational cohort study. | 41 |
| Chapter 4 | Distinct HbA1c trajectories in a Type 2 Diabetes cohort. | 59 |
| Chapter 5 | Real world evidence of suboptimal blood pressure control in patients with Type 2 Diabetes. | 77 |
| Chapter 6 | Prevalence of use of antidepressants, anxiolytics and hypnotics in people with Type 2 Diabetes: the Diabetes Care System (DCS) cohort, West-Friesland, the Netherlands. | 95 |
| Chapter 7 | Primary care physicians related barriers to implementation of a web-based guided insulin self-titration program in people with Type 2 Diabetes. | 109 |
| Chapter 8 | Amsterdam Tool for clinical medication review: development and testing of a comprehensive tool for pharmacists and general practitioners. | 121 |
| Chapter 9 | General Discussion | 145 |
| Chapter 10 | Summary | 161 |
| | Nederlandse Samenvatting | 165 |
| | List of publications | 171 |
| | Dankwoord | 175 |
| | Curriculum Vitae | 183 |

Chapter 1

General Introduction



TREATMENT GOALS AND TREATMENT STRATEGIES IN DIABETES MELLITUS

Diabetes can be classified in type 1 diabetes and type 2 diabetes mellitus (T2DM). Type 1 diabetes is often defined as insulin-dependent diabetes and accounts for 5-10% of all diabetes cases. T2DM is defined as non-insulin-dependent diabetes and accounts for 90-95% of all diabetes cases [1]. T2DM is due to a progressive insulin secretory defect on the background of insulin resistance and deficient beta-cell function [1,2].

The diagnosis of T2DM is based on fasting glucose levels (FPG, threshold ≥ 7.0 mmol/mL) or an oral glucose tolerance test (OGTT, threshold 2-hour plasma glucose ≥ 11.1 mmol/L). Since 2010 the guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have recommended to assess the Hemoglobin A1c (HbA1c) levels, with a threshold of ≥ 48 mmol/mol (6.5%) [1].

With regard to treatment of people with T2DM, the recommended target HbA1c values by ADA/EASD are ≤ 53 mmol/mol (7.0%) [3,4]. Not reaching a target HbA1c value has been shown to increase the risk of diabetes-related complications such as microalbuminuria, retinopathy and mortality [1,5-7].

In the Netherlands, physicians in primary care treat people with T2DM in accordance with the Dutch guidelines, issued by the Dutch College of General Practitioners (NHG guideline T2DM) [8]. The Dutch guidelines are very similar to the ADA/EASD guidelines. Treatment generally starts with lifestyle management which includes weight control by a diet, smoking cessation and an increase of physical activity. If lifestyle management does not lead to the anticipated HbA1c goals, drug treatment with glucose lowering agents is indicated [1,4,8].

The first choice of drug treatment is straightforward, with agreement among leading guidelines: people are prescribed metformin monotherapy [8,9]. When HbA1c levels remain too high, a second oral glucose lowering agent is indicated. In the Netherlands this implies that people with T2DM are prescribed the sulphonylurea (SU) derivative gliclazide [8]. However, in contrast to this one-size-fits all approach in the Dutch guidelines, the ADA/EASD guidelines recommend a more diverse approach suggesting to prescribe GLP-1 receptor agonists, DPP4 inhibitors or SGLT2 inhibitors [1]. The Dutch guidelines are much more reticent in the use of DPP4 inhibitors, GLP1 receptor agonists and SGLT2 inhibitors [1]. The ADA/EASD guidelines provide the primary care physician with an option of triple therapy with three oral glucose lowering agents instead of insulin initiation [1]. In contrast, the Dutch guidelines suggest to start using insulin when the patient does not reach the HbA1c target level with the combination of two oral agents.

INSULIN INITIATION

Three types of insulin, based on the onset of action, are presently available: fast-acting insulin, intermediate-acting insulin and long-acting insulin. The intermediate-acting Neutral Protamine Hagedorn (NPH) insulin is usually prescribed once daily in conjunction with metformin [8]. Using NPH insulin the majority of people reaches acceptable HbA1c levels [8]. However, several barriers for starting to use insulin exist, to patients and primary care physicians alike. They include the risk of hypoglycaemia, weight gain and injection side reactions [10]. This reluctance may lead to a delay in the timing of insulin [11-14]. A recent review of the literature showed that nurses and non-specialized physicians were more reluctant to initiate insulin in a timely manner than physicians specialized in diabetes suggesting that a lack of expertise may account for this reluctance [15]. This might be an opportunity for other health care professionals (read community pharmacists) to take action and show their skills in T2DM management and support the existing diabetes team to optimize their work.

EARLY INITIATION OF INSULIN

Evidence suggests that early initiation of insulin therapy may slow T2DM progression and reduce the risk of long-term complications through preservation of remaining β -cell function [5-7]. Nearly 80% of the people with T2DM in the United Kingdom Prospective Diabetes Study (UKPDS) required insulin during nine years of follow-up to reach HbA1c targets [16,17]. The UKPDS showed that people with T2DM who initiated insulin earlier, had better long-term glucose control than those who remained on the conventional therapy with oral glucose lowering agents [16]. Two other studies performed in Germany and the UK showed that most of the improvement in glycaemic control was achieved during the first year after insulin initiation with little further improvement thereafter, despite changes in insulin dose [17,18]. Lower initial HbA1c levels at the time of insulin initiation were found predictive of a favourable response (i.e. HbA1c < 53 mmol/mol (7.0%)) to insulin therapy within six months [19]. In another study in which a favourable response to insulin was defined as achieving a HbA1c < 58 mmol/mol (7.5%) or a HbA1c lowering of > 1%, responders to insulin were older, had a lower BMI, and higher initial HbA1c levels [20].

Initiating insulin to people with T2DM treated with one oral glucose lowering agent resulted in greater HbA1c reductions and a lower risk of hyperglycaemia than adding insulin to treatment with two or more oral glucose lowering agents [21].

DELAY OF INSULIN INITIATION

Nevertheless, the timing of insulin is often delayed [11-14]. Nichols et al. studied the proportion of people with T2DM attaining and maintaining the glycemic target of 64 mmol/mol (8.0%)

treated with oral glucose lowering agents and the possible initiation of insulin [11]. Even with the less strict target (64 mmol/mol (8.0%)) as compared to the ADA/EASD targets, only 41.9% of these people with T2DM initiated insulin during a mean follow up of 4.6 years [11]. Other studies reported a proportion varying from 40-60% of people with T2DM that initiated insulin and a time to insulin initiation varying from 2-8 years [11-14]. These studies only addressed insulin initiation, and not intensification of the oral glucose lowering drugs. Furthermore, observational studies on the long-term effects of a delayed or timely insulin initiation, with respect to glycaemic control, microvascular complications and mortality are not available.

TRAJECTORIES OF GLYCEMIC CONTROL AFTER INSULIN INITIATION

Despite the benefits of insulin initiation on glycemic control on a population level, the long-term effects of insulin treatment on glycemic control and the achievable glycemic control may differ across subgroups of people with T2DM. Prospective observational population based studies are needed to better understand the factors that may influence glycaemic control in people with T2DM treated with insulin. Investigating long term glycaemic control of people with T2DM treated with insulin by analysing trajectories of HbA1c levels after the start of insulin treatment over time may help to characterize persons for whom personalized medication use strategies are needed to reach their HbA1c targets, or even a more personalized HbA1c target which is optimal in their situation.

EFFECTIVENESS OF TREATMENT STRATEGIES ON CO-MORBIDITIES IN DIABETES MELLITUS

Apart from the treatment of high glucose levels in people with T2DM other cardiovascular risk factors, like hypertension and other co-morbidities (such as depression) should be treated as well.

Hypertension

Cardiovascular disease (CVD) is a highly prevalent co- morbidity and major cause of mortality in people with T2DM. With hypertension being a major risk factor for cardiovascular disease [22], it therefore should be identified and treated in people with T2DM. Life style recommendations including weight loss, smoking cessation and more physical activity should be provided. When ineffective, pharmacological treatment should comprise an ACE-inhibitor or an AT2-antagonist. Multiple drug therapy is often required to achieve blood pressure targets in people with T2DM [1].

Up until now, there is only limited data from observational studies in clinical care available on the association between hypertension, complications and cardiovascular disease mortality in people with T2DM. Little is known about heterogeneity in the course of blood pressure levels in these

people with T2DM. Identifying subgroups of people with T2DM with distinct trajectories of blood pressure levels is important in order to eventually improve their T2DM treatment and may provide more accurate insights into the relationship between blood pressure levels and outcomes.

Depression

In addition to CVD, depression is a second highly prevalent co-morbidity. It is present in approximately 20% of the people with T2DM [23]. Depression has been found to increase the risk of developing T2DM and vice versa [24-26]. The same holds true for anxiety and sleep problems. Depression, sleep problems and anxiety are usually treated by prescribing antidepressants, anxiolytics and hypnotics, which are some of the most often prescribed drugs in Western Society [27-29]. In the general population, antidepressants were prescribed to 6% of the general population. 7.5-9.9% were prescribed anxiolytics and hypnotics [30,31]. However, no data is available on the use of antidepressants, anxiolytics and hypnotics in people with T2DM. Although some studies suggest that antidepressants have a detrimental effect on glycaemic control, insight in the use of antidepressants, anxiolytics and hypnotics is important in order to eventually improve the treatment strategies in depression.

OPTIMIZATION OF GUIDELINES; MORE PERSONALIZED CARE

For decades the recommended stepwise guidelines for treatment of T2DM have not changed much. Over the years more options for treatment with oral glucose lowering drugs have been introduced [32,33]. In 2012 the ADA/EASD guidelines started to recommend personalized medication use for people with T2DM, also known as the patient-centered approach [33]. However, up till now, such strategies on personalized medication use are scarce. In 2013, the Dutch NHG guidelines attempted to provide different strategies of personalized medication use for older people with T2DM. Thus, a target HbA1c level of 64 mmol/mol (8.0%) is recommended for persons who are above 70 years of age and have had diabetes for at least 10 years, as compared to the standard level of 53 mmol/mol (7.0%). In addition, for persons older than 70 years and a disease duration shorter than 10 years, the target has been set at 58 mmol/mol (7.5%), whereas the target for the group only on diet or metformin treatment is 53 mmol/mol (7.0%) [8].

The development of such personalized medication use strategies is still in its infancy. The implementation of tailored and more personalized medication use strategies in T2DM requires more research. It should include research on genetic factors influencing the effectiveness of diabetes medication [34]. Furthermore, more observational data are needed to elucidate the long-term effects of personalized medication use strategies on glycemic control in people with T2DM. The present thesis therefore aims to provide greater understanding in treatment goals and the ef-

fectiveness of treatment strategies in a population-based diabetes cohort with long-term follow up in the Netherlands.

MEDICATION USE

In primary care settings the treatment of people with T2DM has become a primary responsibility of the specialized practice nurse with support from the primary care physician (PCP). The community pharmacist, being part of the broader primary care team, sees the people with T2DM on a regular basis when they collect their medication. However, as yet the pharmacist does not have a pre-defined or prominent role in T2DM care [35]. The Royal Dutch Pharmacists Association (KNMP) recently developed a guideline for pharmaceutical T2DM care. The guideline emphasizes the importance of a good collaboration between the practice nurse, PCP and pharmacist. Indeed, the direct integration of pharmacists into a PCP setting positively affected patient outcomes [36-39].

Because people with T2DM use many different medication types, problems with the use of medicines are common. These problems may pose a risk of non-adherence and affect self-management [35]. Safe and effective use of medication is a major public health issue, and a common responsibility of the people with T2DM, PCP and pharmacist [40]. Interventions by community pharmacists have been shown to improve adherence and consequently health outcomes of people with T2DM [40].

In addition to providing information on the use of medication, another way to improve health is by stimulating the people with T2DM to become involved in their treatment.

INTERVENTIONS TO IMPROVE PATIENT INVOLVEMENT

To facilitate and improve diabetes self-management education (DSME), new tools using internet technology are rapidly being developed. These tools range from relatively simple web-based programmes on DSME to apps for T2DM management on smart phones. In general, DSME assists persons and their clinicians in monitoring changes in health and self-care needs, supports persons' efforts to make behaviour changes by promoting health and effective self-care, and enhances communication between persons and potential supports for their disease management [41]. Earlier studies have shown that instructing and allowing people with T2DM to self-adjust insulin doses facilitates the empowering of patients, giving them the confidence to become more involved in their treatment, while allowing greater treatment flexibility [42]. Self-adjustment of the insulin dose (insulin self-titration) is well established in type 1 diabetes suggesting that similar therapeutic self-management may also be beneficial when applied to people with T2DM

[42]. However, as yet DSME in T2DM produced inconsistent results with respect to HbA1c reductions and other clinical outcomes such as weight loss and physical activity [43-46]. Difficulties in e-health self-management implementation are an international phenomenon with a variety of similar problems being widely reported [47-50].

OBJECTIVE

The principal aim of this thesis is to reach a greater understanding in treatment goals and the effectiveness of current treatment strategies in glycemic control in people with T2DM in daily practice. Secondly, the evaluation of an intervention to improve patient involvement and the development of an intervention to optimize T2DM treatment is investigated. Overall, this thesis will contribute to optimization of treatment strategies in people with T2DM.

OUTLINE OF THE THESIS

Oral glucose lowering agents and insulin treatment in T2DM. The first part of this thesis (chapter 2 – 5) focuses on the treatment of T2DM in the real world. The aim was to gain insight in the time to insulin initiation and long term outcomes including glycaemic control, microvascular complications and mortality in people with T2DM not responding to oral glucose lowering agents (**chapter 2**). In addition, subgroups of insulin users (**chapter 3**) and the overall T2DM population (**chapter 4**) with distinct HbA1c trajectories were identified.

Treatment of co-morbidities. The second part of this thesis concerns the management of co-morbidities in people with T2DM. Firstly, we aimed to identify subgroups with distinct trajectories of systolic blood pressure in the overall T2DM population (**chapter 5**). Secondly, the use of antidepressants, anxiolytics and hypnotics in people with T2DM was studied as well as the socio-demographic characteristics and T2DM medication associated with their use (**chapter 6**).

Interventions to improve patient involvement and evaluate treatment strategies. In the last part of this thesis two interventions to improve patient involvement in T2DM treatment are presented and treatment strategies evaluated. Firstly, the feasibility of a web-based guided insulin self-titration in T2DM people was evaluated (**chapter 7**). Secondly, a tool for clinical medication review (**chapter 8**) to facilitate and support the periodic review of (older) patients' medication by community pharmacists and primary care physicians is presented.

Finally, in the general discussion the main findings of the previous chapters in the context of the current literature are reviewed and certain methodological issues discussed. The conclusion addresses future perspectives and the role of the pharmacist in the diabetes management.

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Chapter 2

Time to insulin initiation and long term effects
of initiating insulin in people with Type 2
Diabetes Mellitus: the Hoorn Diabetes Care
System Cohort Study.

Ruth Mast, A.P. Danielle Jansen, Iris Walraven, Simone P. Rauh,
Amber A.W.A van der Heijden, Robert J. Heine, Petra J.M. Elders,
Jacqueline M. Dekker, Giel Nijpels, Jacqueline G. Hugenburg.

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ABSTRACT

Objective The aim of this study was to assess the time to insulin initiation in people with T2DM treated with oral glucose lowering agents and to determine the baseline characteristics associated with time to insulin initiation. This was evaluated in people with T2DM with HbA1c levels consistently ≥ 53 mmol/mol (7.0%) during total follow-up and in those with fluctuating HbA1c levels around 53 mmol/mol (7.0%).

Research Design and Methods Prospective, observational study comprising 2,418 persons with T2DM aged ≥ 40 years who entered the Diabetes Care System, between 1998 – 2012 with a minimum follow-up of at least three years following a first HbA1c level ≥ 53 mmol/mol (7.0%). Cox regression analyses were performed to assess the determinants of the time to insulin initiation. Data related to long term effects of insulin initiation were studied at baseline and end of follow up using descriptive summary statistics.

Results Two-third of the persons initiated insulin during follow up. The time to insulin varied from 1.2 years (range 0.3-3.1) in people with T2DM with HbA1c levels consistently ≥ 53 mmol/mol (7.0%) to 5.4 years (range 3.0-7.5) in people with T2DM with fluctuating HbA1c levels around 7.0%. Longer diabetes duration (HR 1.04 95% CI 1.03-1.05) and lower age (HR 1.00 95% CI 0.99-1.00) at baseline were associated with a shorter time to initiation. More insulin initiators had retinopathy compared to people with T2DM that remained on oral glucose lowering agents during follow up.

Conclusions The time to insulin initiation was short and most of the people with T2DM with HbA1c levels consistently ≥ 53 mmol/mol (7.0%) were initiating insulin. Longer diabetes duration and younger age shortened the time to insulin.

INTRODUCTION

Guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend target HbA1c values of ≤ 53 mmol/mol (7.0%) in the majority of the people with type 2 diabetes mellitus (T2DM) [1,2]. Not reaching the target HbA1c values of ≤ 53 mmol/mol (7.0%) has been shown to increase the risk of diabetes related complications [3-5]. Treatment of people with T2DM initially involves lifestyle changes and therapy with oral glucose lowering agents. In case of an inadequate response to oral glucose lowering agents, treatment with insulin is indicated [1,2,6]. Initiating insulin therapy only after persistent high glucose values is a traditional approach [3]. Evidence suggests that early intensive insulin therapy may slow the progression of diabetes and reduce the risk of long-term complications through preservation of remaining β -cell function [3-5]. The UKPDS study showed that people with T2DM who initiated insulin earlier in the course of diabetes, had better long-term glucose control than those who remained on the conventional therapy with oral glucose lowering agents [7].

Studies in patients inadequately responding to oral glucose lowering agents showed a time to insulin initiation varying from two to eight years [8-10]. However, these studies were retrospective and were generally based on registries from primary care practices (PCPs) prior to 2005. Furthermore, these studies only addressed insulin initiation, and not intensification of the oral glucose lowering treatment. Finally, observational studies on the long term effects of insulin initiation, with respect to glycaemic control, microvascular complications and mortality are not available. Three randomized controlled trials reported that a reduction in HbA1c was associated with a reduction in microvascular complications [7,11,12]. However, these RCTs were performed in relative healthy people with T2DM [7,11,12].

The present prospective, population based study addresses all issues described above and includes annually standardized measurements from people with T2DM during the period between 1998 and 2012.

The aim of this study was to assess the time to insulin initiation in people with T2DM treated with oral glucose lowering agents and to determine the baseline characteristics associated with time to insulin initiation. This was evaluated in people with T2DM with HbA1c levels consistently ≥ 53 mmol/mol (7.0%) and in those with fluctuating HbA1c levels around 53 mmol/mol (7.0%) separately. An exploratory aim was to evaluate long term outcomes, including glycaemic control, microvascular complications and mortality.

RESEARCH DESIGN AND METHODS

Study population

A prospective, observational study was performed using data from the Diabetes Care System in the period between 1998 and 2012, described in detail elsewhere [13,14]. In short, the Diabetes Care System provides diabetes care in the region of West-Friesland in the Netherlands, a region with about 200,000 inhabitants that is representative of a Western-European population [15].

The Diabetes Care System uses a managed care plan for T2DM with contracted health care providers and is responsible for the quality of diabetes care in the region. Diabetes care encompasses the care provided by a patient's PCP, according to the Dutch treatment guidelines for T2DM [16], the annual assessment as organized centrally by the Diabetes Care Centre for annual review and patient education by the diabetes nurse and dietician. Results of the assessment and protocol-driven therapeutic advice are provided to the patient's PCP [17]. Patients are included in the Diabetes Care System 1.45 years (range 0.3 to 5.3) after the clinical diagnosis.

For each patient, the year of entry was considered as the baseline measurement (T0). The Diabetes Care System maintains anonymized computer records and the patients were informed of the use of these records for research purposes.

Participants

All 2,418 people with T2DM aged 40 years and over (to exclude people with type 1 diabetes), with at least three follow up moments after the first HbA1c level ≥ 53 mmol/mol (7.0%) and with a mean HbA1c level ≥ 53 mmol/mol (7.0%) during follow up and not using insulin before entry in the Diabetes Care System were extracted. People with T2DM that were already using insulin at the baseline measurement were excluded. Participants included in this study had a follow-up period ranging from 3 to 14 years.

Measurements

HbA1c was assessed with a DCCT standardized reversed-phase cation exchange chromatography (HA 8160 analyzer, Menarini, Florence, Italy). HbA1c was detected using a dual-wavelength colorimetric (415-500). The intra-assay coefficient of variation (CV) was 0.6% at a mean level of 4.9% and the inter-assay CV was 0.8% at a mean level of 5.5%.

Weight and height were measured annually (while patients were barefoot and wearing light clothing). *BMI* was calculated (weight in kilograms divided by the square of height in meters). *Diabetes duration* was self-reported and was divided into four groups: a diabetes duration of 0 - 2 years, of 2 - 5 years, of 5 - 10 years and of 10 years or longer. The diabetes duration was verified at

the PCP practice. Diabetes management differs across PCPs and by the employment of a nurse practitioner (NP) for diabetes management. Therefore, PCP organizations were categorized into three types: 1) involvement of a nurse practitioner in diabetes management, the insulin is initiated by the PCP; 2) involvement of a nurse practitioner and insulin was initiated by the Diabetes Care System; 3) no nurse practitioner and insulin was initiated by the Diabetes Care System. At any time, the PCP organization has the opportunity to send a patient to the Diabetes Care System for the initiation of insulin. In the Netherlands patients are obliged to choose a PCP based on the geographical location of the PCP and they might choose a PCP within the geographical location on the basis of their preferences, e.g. involvement of a nurse practitioner.

Blood pressure was measured annually. Systolic and diastolic blood pressure were measured on the right arm after 5 minutes of rest in a seated position with the oscillometric device, Colin 8800C between 2003 and 2011. After 2011, the oscillometric device, Welch Allyn monitor was used. Glucose (fasting and 2-hr after the OGTT) was measured in venous plasma using the glucose-oxidase method (Glucoquant/hexokinase/G6P-DH;Boehringer Mannheim, Mannheim,Germany). *Triglycerides, total and HDL-cholesterol* were determined from fasting blood samples using enzymatic techniques (Boehringer Mannheim, Mannheim, Germany). *LDL-cholesterol* was estimated using the Friedewald formula, except in subjects with triglycerides > 4.5 mmol/l. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula.

Microalbuminuria was considered present if UACR > 2.0 mg/mmol. *Retinopathy* (fundus photography of both eyes was performed yearly) was measured from 1998 until 2000, with a Kowa Pro Fundus camera with a green filter (Kowa Optical Industry, Torrance, CA). Black and white, 35-mm photographs were taken 30 min after mydriasis with 0.5% tropicamide and 2.5% phenylephrine eye drops. From the beginning of 2000 until 2004, fundus photography of both eyes was performed with a nonmydriatic Canon CR5 camera (Canon Inc., Tokyo, Japan). From 2004, fundus photography of both eyes was performed using a nonmydriatic Topcon TRC NW 100 camera (Topcon, Tokyo, Japan). All participants were examined using 45-degree fundus photographs. One photograph was centred on the macula and the other nasally with one optic disc diameter from the temporal side. All photographs were graded by an experienced ophthalmologist according to the EURODIAB classification score [18]. The retinopathy at the end of follow up is calculated for each person at the end of her/ his follow up period. All measurements were performed at the clinical chemistry laboratory at the Westfries Gasthuis in Hoorn (the Netherlands).

Information on *current medication use* was registered yearly at the annual visit by checking dispensing labels brought by people with T2DM. Three different groups of oral glucose lowering agents were defined: metformin, sulphonylurea (SU) and other oral glucose lowering agents.

The other oral glucose lowering agents category contains the following groups of oral glucose lowering agents : thiazolidinediones, alfa glucosidase inhibitors, DPP4 inhibitors, meglitinides and GLP-1 receptor agonists.

Mortality was derived from the municipal administration registries updated every three months. Information on the cause of death was retrieved from medical records of general practitioners and from the local hospital.

Statistical analyses

At first, two groups were defined; one group that initiated insulin during follow up and one group that remained on oral glucose lowering agents. Moreover, within these groups we distinguished persons with HbA1c levels **consistently** ≥ 53 mmol/mol (7.0%) and **fluctuating** HbA1c levels around 53 mmol/mol (7.0%). Persons with all HbA1c measurements ≥ 53 mmol/mol (7.0%) during total follow up were defined as 'consistently ≥ 53 mmol/mol (7.0%)'; people with T2DM with HbA1c measurements fluctuating around 53 mmol/mol (7.0%) were defined as 'fluctuating around 53 mmol/mol (7.0%)'.

Baseline characteristics (i.e. age, sex, BMI, diabetes duration, HbA1c, SBP, fasting glucose, total cholesterol, HDL cholesterol, triglycerides and oral glucose lowering agents) of the four groups were studied using descriptive summary statistics. Baseline characteristics of insulin initiators vs. no insulin initiators were tested for differences with One-Way ANOVA and post hoc Bonferroni tests for mean levels, with Chi-square tests for proportions and Kruskal-Wallis test for median levels in the study population.

The time to insulin initiation was calculated as the time between the first HbA1c level higher than 53 mmol/mol (7.0%) and the time to insulin initiation. Mean HbA1c levels over time in the groups were plotted in a graph. The number of oral glucose lowering agents used at baseline and end of follow up was calculated. If people with T2DM were initiating insulin during follow up, the number of oral glucose lowering agents before the initiation of insulin was registered.

A Cox proportional hazards model was used to determine which characteristics at baseline (i.e. BMI, Glucose, PCP organisation, SBP, HbA1c and diabetes duration) were associated on the timing of insulin initiation. All analyses were adjusted for age and sex. All determinants with p-values < 0.10 were entered simultaneously using a backward elimination method, leading to a model including only significant ($p < 0.05$) determinants. Before the model was constructed, the proportional hazard assumption, i.e. that the hazard ratio is constant over time, was tested by comparing estimated log-log survival curves for all covariates. All continuous variables were divided into quartiles to check whether or not these variables met the proportional hazard assumption. All

assessed log-log survival plots graphically showed two parallel lines, indicating no violation of the assumption.

We repeated the Cox regression analysis stratifying for HbA1c levels: in people with T2DM with HbA1c levels **consistently** ≥ 53 mmol/mol (7.0%) and with HbA1c levels **fluctuating** around ≥ 53 mmol/mol (7.0%). Data are presented as Hazard Ratios (HR) with a 95% confidence interval (CI). P-values lower than 0.05 were considered statistically significant.

Data related to long term consequences of insulin initiation (mortality, retinopathy and microalbuminuria) were studied at baseline and end of follow up using descriptive summary statistics. Statistical analyses were performed using SPSS for Windows (version 20.0, SPSS Inc., Chicago, IL).

RESULTS

Figure 1 shows the flow chart of the T2DM population analysed in this study. A total of 8,308 persons with T2DM participated in the Diabetes Care System. For the current study, 2,418 people with T2DM with an HbA1c ≥ 53 mmol/mol (7.0%) were included.

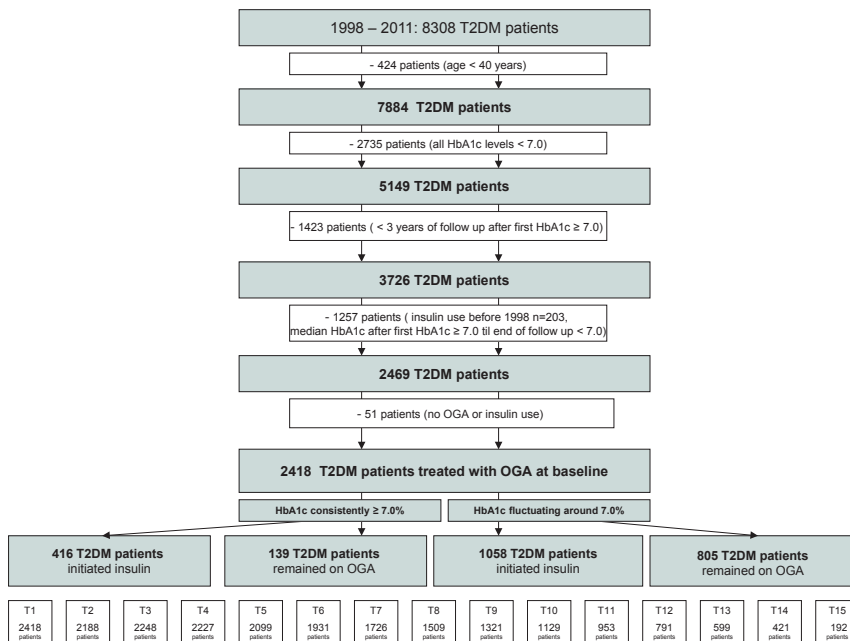


Figure 1. Flowchart of the included people with T2DM.

Baseline characteristics

Table 1 shows baseline characteristics of the four subgroups of people with T2DM. In total, 1,474 persons (61.0%) initiated insulin and 944 persons (39.0%) remained on oral glucose lowering agents during follow up. In total, 555 (23%) people with T2DM had HbA1c levels consistently higher than ≥ 53 mmol/mol (7.0%) (group 1A and 1B) and 1,863 (77%) people with T2DM had HbA1c levels fluctuating around 53 mmol/mol (7.0%) during follow up (group 2A and 2B).

Table 1. Baseline characteristics, at entry in the diabetes care system of the study population.

| | HbA1c consistently ≥ 53 mmol/mol (7.0%) | | HbA1c fluctuating around 53 mmol/mol (7.0%) | |
|--|--|-----------------------|---|-------------------------------|
| | Group 1A | Group 1B | Group 2A | Group 2B |
| | Insulin initiation | No insulin initiation | Insulin initiation | No insulin initiation |
| Number of persons with T2DM | 416 | 139 | 1058 | 805 |
| Age (yr) | 61.2 \pm 10.4 | 62.5 \pm 11.6 | 60.8 \pm 10.4 [^] | 61.9 \pm 10.5 [^] |
| Sex (male %) | 52.6 | 51.1 | 51.1 [^] | 57.9 [^] |
| BMI (kg/m ²) | 29.9 \pm 5.5 | 30.4 \pm 5.3 | 29.9 \pm 5.6 [^] | 30.4 \pm 5.5 [^] |
| Diabetes duration at entry in DCS (yr) | 2.5 (0.3 – 7.0)* | 1.2 (0.3 – 4.0)* | 2.1 (0.4 – 6.6) [^] | 0.8 (0.2 – 2.7) [^] |
| HbA1c (mmol/mol) | 69 \pm 1.9* | 63 \pm 1.5* | 65 \pm 1.8 | 66 \pm 1.8 |
| SBP (mmHg) | 141.7 \pm 21.0 | 143.8 \pm 22.6 | 142.0 \pm 21.2 [^] | 144.0 \pm 20.5 [^] |
| Fasting glucose (mmol/L) | 10.3 \pm 2.8* | 9.1 \pm 2.6* | 9.8 \pm 3.9 [^] | 9.2 \pm 2.4 [^] |
| Total cholesterol (mmol/L) | 5.4 \pm 1.2 | 5.4 \pm 1.3 | 5.4 \pm 1.2 | 5.3 \pm 1.1 |
| HDL cholesterol (mmol/L) | 1.19 \pm 0.3 | 1.21 \pm 0.4 | 1.20 \pm 0.4 | 1.20 \pm 0.3 |
| Triglycerides (mmol/L) | 2.20 \pm 1.7 | 2.15 \pm 1.3 | 2.25 \pm 3.3 | 2.01 \pm 1.2 |
| Microalbuminuria (%) | 21.4 | 18.0 | 19.3 | 19.4 |
| Any Retinopathy (%) | 15.6 | 8.1 | 12.1 | 9.2 |
| Grade 1 Retinopathy (%) | 11.0 | 3.6 | 8.2 | 6.6 |
| Grade 2 Retinopathy (%) | 2.8 | 3.6 | 2.2 | 1.4 |
| Grade 3 Retinopathy (%) | 1.5 | 0.9 | 1.2 | 0.9 |
| Grade 4 Retinopathy (%) | 0.3 | 0.0 | 0.5 | 0.3 |
| Metformin use only (%) | 16.3* | 30.2* | 24.4 [^] | 35.9 [^] |
| SU use only (%) | 27.6 | 20.1 | 24.4 [^] | 19.9 [^] |
| Metformin + SU use only (%) | 34.1* | 23.7* | 20.3 [^] | 12.4 [^] |
| Other combination (%) | 4.3 | 2.2 | 2.4 | 1.9 |
| Unknown medication (%) | 17.7 | 23.8 | 28.5 | 29.9 |
| Time to insulin (yr) | 1.2(0.3 – 3.1)# | | 5.4 (3.0 – 7.5)# | |

Table 1. Baseline characteristics, at entry in the diabetes care system of the study population. (continued)

| | HbA1c consistently ≥ 53 mmol/mol (7.0%) | | HbA1c fluctuating around 53 mmol/mol (7.0%) | |
|-------------------------------|--|-----------------------|---|----------------------------|
| | Group 1A | Group 1B | Group 2A | Group 2B |
| | Insulin initiation | No insulin initiation | Insulin initiation | No insulin initiation |
| End of follow up | | | | |
| Follow up (yr) | 8.8 \pm 3.3* | 4.9 \pm 2.4* | 8.9 \pm 3.3 [^] | 7.1 \pm 3.0 [^] |
| Metformin use only (%) | 25.2* | 15.8* | 29.4 [^] | 18.8 [^] |
| SU use only (%) | 14.4* | 1.4* | 6.0 [^] | 4.0 [^] |
| Metformin + SU use only (%) | 36.3 | 44.6 | 36.5 [^] | 53.9 [^] |
| Other combination (%) | 3.8 | 7.2 | 6.4 [^] | 11.7 [^] |
| Unknown medication (%) | 20.3 | 31.0 | 21.7 | 8.8 |
| Long term consequences | | | | |
| Microalbuminuria (%) | 30.4 | 25.9 | 27.7 | 24.5 |
| Any Retinopathy (%) | 12.1 | 12.2 | 11.3 [^] | 6.8 [^] |
| Grade 1 Retinopathy (%) | 6.3 | 8.4 | 6.7 | 4.3 |
| Grade 2 Retinopathy (%) | 2.6 | 1.5 | 1.7 | 1.0 |
| Grade 3 Retinopathy (%) | 0.8 | 0.8 | 0.8 | 0.5 |
| Grade 4 Retinopathy (%) | 2.4 | 1.5 | 2.1 | 1.0 |
| Mortality (%) | 21.4 | 27.3 | 18.0 | 21.2 |

Abbreviations: BMI: body mass index, SBP: systolic blood pressure, OGA: oral blood glucose lowering agents. Data as mean \pm standard deviation or median (interquartile range). * indicates a statistical significant difference in group 1A vs. group 1B, [^] indicates a statistical significant difference in group 2A vs. group 2B ($p < 0.05$), # indicates a statistical significant difference in group 1A vs. group 2A ($p < 0.001$).

Time to insulin

416 (75%) people with T2DM with HbA1c levels consistently higher ≥ 53 mmol/mol (7.0%) initiated insulin (group 1A) in a median time of 1.2 years (range 0.3-3.1), and 1,058 (56.8%) people with T2DM with levels fluctuating around 53 mmol/mol (7.0%) initiated insulin (group 2A) in a median time of 5.4 years (range 3.0 – 7.5).

Insulin initiation vs. no insulin initiation

Insulin initiators were younger (60.9 years vs. 62.0 years), had lower BMI levels (29.9 kg/m² vs. 30.4 kg/m²), higher glucose levels (9.9 mmol/L vs. 9.2 mmol/L), and a longer diabetes duration (2.2 years vs. 0.9 years) compared to persons that remained on oral glucose lowering agents.

Intensification of treatment in people with T2DM initiating insulin

At baseline, persons in group 1A used 1 (45.0%), 2 (37.0), or 3 (0.5%) oral glucose lowering agents. During follow up, the number of oral glucose lowering agents was increasing. Before the initiation

of insulin 29.8% of these patients was using one oral glucose lowering agent, 57.5% was using two oral glucose lowering agents, and 1.0% was using three oral glucose lowering agents. Persons in group 2A used at baseline 1 (49.1%), 2 (21.6%), or 3 (0.8%) oral glucose lowering agents. In this group the number of oral glucose lowering agents increased during follow up. Before the initiation of insulin patients used 1 (33.6%), 2 (43.5%) or 3 or more (2.4%) oral glucose lowering agents.

At initiation of insulin, 11.1% of the patients in group 1A used only metformin, 18.5% only SU, 54.8% a combination of metformin and SU, and 3.8% another combination of oral glucose lowering agents. In group 2A, 22.9% of the patients were using only metformin, 10.0% only SU, 40.9% a combination of metformin and SU, and 5.7% another combination of oral glucose lowering agents.

Intensification of treatment in people with T2DM remaining on oral glucose lowering agents

During follow up the PCPs intensified the treatment with oral glucose lowering agents in group 1B and 2B (see Table 1). 15.8% of the 139 people with T2DM in group 1B used only metformin, 1.4% used only SU, 44.6% used a combination of metformin and SU, and 7.2% used another combination of oral glucose lowering agents at the last follow up moment. Persons in group 2B used only metformin (18.8%) at the last follow up moment, 4.0% only SU, 53.9% a combination of metformin and SU, and 11.7% another combination of oral glucose lowering agents.

Baseline characteristics associated with time to insulin initiation

Table 2 presents the Cox regression models for the time to insulin initiation in people with T2DM. Longer duration of diabetes (HR 1.04 95% CI 1.03 – 1.05) and lower age (HR 1.00 95% CI 0.99 – 1.00) were associated with a shorter time to insulin in people with T2DM. Stratifying for people with T2DM with HbA1c levels consistently ≥ 53 mmol/mol (7.0%) higher glucose levels (HR 1.10 95% CI 1.06 – 1.14) at baseline were associated with a shorter time to insulin. In people with T2DM with HbA1c levels fluctuating around 53 mmol/mol (7.0%) longer duration of diabetes (HR 1.04 95% CI 1.03 – 1.05) at baseline was associated with a shorter time to insulin. PCP organization was not associated with time to insulin initiation in any of the groups.

Long term consequences of insulin initiation

At baseline, no differences were found in microalbuminuria and retinopathy between people with T2DM initiating insulin compared to persons that remain on oral glucose lowering agents. At the end of follow up (mean follow up 5.3 year, SD 3.4) there were statistically significant more patient with microalbuminuria and retinopathy in insulin initiators compared to patients that remain on oral glucose lowering agents (microalbuminuria: 28.4% vs. 24.7%, retinopathy: 11.6% vs. 7.7%). The total mortality (n= 209 vs. n= 279) in people with T2DM that remain on oral glucose

Table 2. Cox proportional hazard model of the time to insulin in people with type 2 diabetes mellitus treated with oral glucose lowering agents.

| Overall population | | |
|---|---------------------------|------------------|
| | HR (95% CI) | P level |
| Sexe (female vs. male) | 1.06 (0.95 – 1.18) | 0.28 |
| Age (yr) | 1.00 (0.99 – 1.00) | <0.001 |
| Diabetes duration (yr) | 1.04 (1.03 – 1.05) | 0.05 |
| Patients with HbA1c levels consistently ≥ 53 mmol/mol (7.0%) (Group 1A&1B) | | |
| | HR (95% CI) | P level |
| Sexe (female vs. male) | 0.96 (0.79 – 1.17) | 0.67 |
| Age (yr) | 1.00 (0.99 – 1.01) | 0.65 |
| Glucose (mmol/L) | 1.10 (1.06 – 1.14) | <0.001 |
| Patients with fluctuating HbA1c levels around 53 mmol/mol (7.0%) (Group 2A&2B) | | |
| | HR (95% CI) | P level |
| Sexe (female vs. male) | 1.10 (0.97 – 1.24) | 0.15 |
| Age (yr) | 0.99 (0.99 – 1.00) | 0.06 |
| Diabetes duration (yr) | 1.04 (1.03 – 1.05) | <0.001 |

Abbreviation: HR = Hazard Ratio.

lowering agents was statistically significantly higher compared to patients that initiate insulin during follow up (22.1% vs. 18.9%, $p=0.05$). After adjustment for baseline HbA1c the relationship for microalbuminuria and mortality disappeared, but did not materially changed the results for retinopathy.

No differences were found in microalbuminuria, retinopathy and mortality at baseline and at the end of follow up in persons of group 1A and 1B. There were statistically significant more persons in group 2A with retinopathy at the end of follow up compared to persons in group 2B (27.7% vs. 24.5%). No differences were found in microalbuminuria and mortality between group 2A and group 2B.

HbA1c levels over time

Figure 2 represents the HbA1c levels over time in the different groups of people with T2DM. Group 1B shows the worst course of HbA1c levels over time, with HbA1c levels that remain above the 59 mmol/mol (7.6%) during the first 10 years of follow up. People with T2DM in group 2B showed HbA1c levels of around 55 mmol/mol (7.2%).

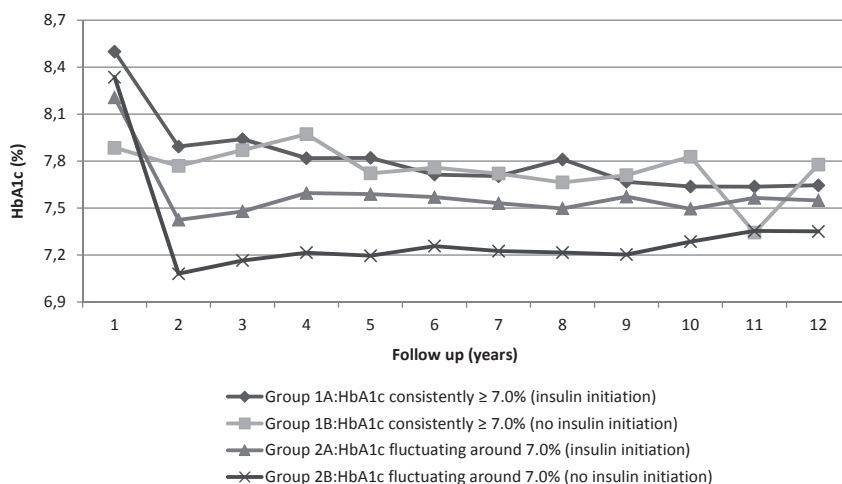


Figure 2. HbA1c levels over time in the four groups of people with T2DM.

DISCUSSION

Insulin therapy was initiated in 61% of the 2,418 included people with T2DM treated with oral glucose lowering agents during follow up. The time to insulin varied from 1.2 years (range 0.3-3.1) in persons with HbA1c levels consistently ≥ 53 mmol/mol (7.0%) to 5.4 years (range 3.0 – 7.5) in persons with fluctuating HbA1c levels around 53 mmol/mol (7.0%). Longer duration of diabetes at baseline was associated with a shorter time to insulin initiation. People with T2DM that initiated insulin during follow up had more retinopathy compared to people with T2DM that remain on oral glucose lowering agents during follow up even adjusted for HbA1c.

To our knowledge, this is the first observational study describing subgroups of people with T2DM with HbA1c levels consistently ≥ 53 mmol/mol (7.0%) and fluctuating HbA1c levels around ≥ 53 mmol/mol (7.0%) with a long term follow-up.

Nichols et al. studied the proportion of patients attaining and maintaining the glycemic target of 64 mmol/mol (8.0%) treated with oral glucose lowering agents and the possible initiation of insulin [8]. Even with a less strict target (64 mmol/mol (8.0%)) compared to our study only 41.9% of these patients initiated insulin during a mean follow up of 4.6 years [8]. Other studies reported a proportion varying from 40-60% of patients that initiated insulin and a time to insulin initiation varying from 2-8 years [8-10,19]. However, these studies did not use the ADA/EASD target level of 53 mmol/mol (7.0%), which impedes the comparison with our results. However, it is clear that even with higher HbA1c target levels, the time to insulin initiation in these populations were longer compared to our study. In an earlier study of our group [20], we showed that managed diabetes

care with a central organization and central management of care, was statistically significantly associated with a better process of the diabetes care and lower direct costs compared to usual diabetes care. This persisted after adjustment for differences in patient characteristics at baseline. This could be the explanation that in insulin initiation this centrally managed diabetes care is the reason for a shorter time to insulin initiation. Thereby, care outcomes and glycemic control of this population are usually better than those in other cohorts [1-3] and most likely outcomes would be worse in other populations.

People with T2DM that initiated insulin showed more retinopathy compared to people with T2DM that remain on oral glucose lowering agents during follow up. The exact reason for this is difficult to explain and needs further elaboration. However, the association between deteriorating glycemic control and an increased risk of microvascular complications was reported by many others before [21,22]. After adjustment for HbA1c, there was no difference in mortality between insulin users and people with T2DM that remain on oral glucose lowering agents. These findings are in accordance with results from the VADT study. This study found no effect on the mortality rates in people with T2DM initiating insulin compared to people with T2DM that remain on oral glucose lowering drugs [22].

Observational research is an important complementary approach employed to document how drugs are actually used in routine clinical practice, we have to address some limitations of the present study. The data on medication use might be an underestimation (not all medication is known), because information on medication use was obtained on the basis of self-reporting and no information on the medication dose was available. In the study period of 1998 - 2012 national guidelines were updated. These guidelines were advocating in 1999 first choice treatment of metformin in people with T2DM with a BMI > 27. In 2006 metformin was first choice treatment for all people with T2DM. This could not have affected the results of our study.

Not all known patient, physician, and practice related reasons for possible delay in the time to initiation of insulin, have been measured. For example, we were not able to include patients' psychological insulin resistance, e.g. patients fear of disease progression, needle anxiety, concerns about hypoglycaemia and weight gain, adherence to lifestyle advices and oral glucose lowering medication [8,23]. Moreover, we were not able to include adherence of PCPs with guidelines. Differences in protocol adherence could influence timely insulin initiation. However, we did not find a statistically significant association of PCP practice organisation with timing of insulin initiation. We assume that most PCPs followed the agreed regional diabetes protocol, but we cannot exclude that PCPs felt resistance against insulin initiation in people with fluctuating values around the glycemic target.

Strengths of this study include the prospective, observational design with a long term follow up (up to 14 years), the completeness of the dataset and standardized yearly measurements. Furthermore, we described the intensification of the treatment and long term consequences of insulin initiation. Additionally, the study population was larger ($n=2,418$) than most of the previously published studies on this subject. Finally, all people with T2DM in the described region are referred to the Diabetes Care System and, therefore, biased referral of the most complex people with T2DM to secondary care is unlikely to have occurred.

Our findings urge additional studies examining the benefits of an earlier initiation of insulin therapy. In addition, further research is needed to understand the clinician, patient, and system related barriers to insulin initiation in order to design strategies targeted at modifying barriers to insulin initiation.

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Chapter 3

Effectiveness of insulin therapy in people with Type 2 Diabetes in the Hoorn Diabetes Care System.



Ruth Mast, Iris Walraven, Trynke Hoekstra, A.P. Daniëlle Jansen, Amber A. van der Heijden,
Petra J.M. Elders, Robert J. Heine, Jacqueline M. Dekker, Giel Nijpels,
Jacqueline G. Hugtenburg.

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ABSTRACT

Objective Glycemic control trajectories following the initiation of insulin therapy and the determinants of a good response to insulin therapy are not well characterised. The main aim of the current study was to identify HbA1c trajectories following the start of insulin treatment. An exploratory objective was to identify clinically applicable predictors of the response to insulin therapy.

Research design and methods The study population comprised 1,203 people with type 2 diabetes out of the Diabetes Care System (DCS) (n= 9,849). Inclusion criteria: aged ≥ 40 year, initiated insulin during follow up after failure to reach HbA1c levels ≤ 53 mmol/mol (7%) with oral glucose lowering agents, and a follow up ≥ 2 years after initiating insulin. Latent Class Growth Modelling (LCGM) was used to identify trajectories of HbA1c. We defined 'off-target' when HbA1c levels were 53 mmol/mol (7.0%) or higher in 1/3 or more of the follow-up time, and 'on-target' when HbA1c levels were 53 mmol/mol (7.0%) or higher in less than 1/3 of the follow up time.

Results Four HbA1c trajectories were identified. Most people were classified in a stable HbA1c trajectory of around 57 mmol/mol (7.4%) (88.7%). Only 24.4% of the people were 'on-target' to insulin, this was associated with lower HbA1c levels and higher age at the start of insulin treatment.

Conclusions With LCGM four HbA1c trajectories were identified. A quarter of the people starting insulin were 'on-target'. Low HbA1c levels and advanced age at the start of insulin therapy were associated with better response to insulin therapy. Initiating insulin earlier improves the likelihood of achieving and sustaining glycemic control.

INTRODUCTION

The guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) for the management of type 2 diabetes (T2DM) recommend target HbA1c levels of ≤ 53 mmol/mol (7.0%) in the majority of people with T2DM [1,2].

Most people with T2DM require insulin treatment in the course of the disease to achieve these HbA1c targets [3,4]. Because of the progressive nature of T2DM, many people show a pattern of so-called 'serial failure' as a result of sequential addition of glucose lowering drugs including insulin as the final step and only a minority of these people are able to achieve HbA1c levels ≤ 53 mmol/mol (7.0%) [5,6]. A recent 24 month retrospective database analysis showed that most of the improvement in glycemic control was achieved in the first six months following insulin initiation with little further improvements thereafter, despite changes in insulin dose [7].

One study showed that lower initial HbA1c levels at the time of insulin initiation predict a favourable response (HbA1c < 53 mmol/mol (7.0%)) to insulin therapy within six months [8]. Another study defined the response to insulin as achieving a HbA1c < 58 mmol/mol (7.5%) or a HbA1c lowering of $> 1\%$. Responders to insulin were older, had a lower BMI, and higher initial HbA1c levels [9]. The latter finding may be due to the applied definition of responder, which also included the magnitude of HbA1c response. Moreover, these studies were retrospective and had a short follow up with a maximum of 2 years [8,9]. For clinical practice it is important to understand the factors predicting long-term effectiveness of insulin therapy. RCTs have their limitations as they are often conducted in relatively healthy people with T2DM under strictly controlled circumstances with a short follow up. Prospective observational population based studies are needed to better understand the factors that may affect glycaemic control in people with T2DM treated with insulin.

In this study we aimed to analyse the long term glycaemic control of people with T2DM treated with insulin by analysing trajectories of HbA1c levels after the start of insulin and by analysing the sustainability of HbA1c levels over time. An additional objective was to identify clinically applicable predictors of the response to insulin initiation.

RESEARCH DESIGN AND METHODS

Study Population

An observational population based cohort study was performed with data from the West-Friesland Diabetes Care System, described in detail elsewhere [10]. Briefly, the Diabetes Care System organizes the diabetes care in the region of West-Friesland in the Netherlands, a region

with about 200,000 inhabitants and representative for a Western-European population [11]. Of all people with T2DM in this region 96% participated in the Diabetes Care System.

The services provided by Diabetes Care System encompass direction to the patient's primary care physician (PCP) in accordance with the Dutch guidelines for T2DM, an annual assessment at the Diabetes Care System including HbA1c monitoring, and patient education by nurses and dietitians [12]. People entered the Diabetes Care System in different years and with different diabetes durations. The year of initiating insulin was considered the year of entry in this study (T0). All people were informed and agreed to the use of these records for research purposes.

Study participants

In the period between 1998 and 2012, 9,849 people with T2DM entered the Diabetes Care System. For the current study, 1,203 people with T2DM, who initiated insulin during follow up were selected from the Diabetes Care System. These people aged 40 years and over, and had a follow up of at least two years after initiation of insulin.

Confirmation of diabetes and diabetes duration

The date of diabetes diagnosis was self-reported and confirmed in the records of the PCP if at least one of the following was reported: 1) one or more classic symptoms plus one fasting plasma glucose ≥ 7.0 mmol/l or random plasma glucose ≥ 11.1 mmol/l; 2) at least two elevated plasma glucose concentrations on different occasions (fasting glucose ≥ 7.0 mmol/l or random plasma glucose ≥ 11.1 mmol/l) in the absence of symptoms. Diabetes duration was calculated from the date of diabetes diagnosis until the date of insulin initiation.

Measurements

HbA1c levels were assessed with a DCCT standardized reversed-phase cation exchange chromatography HA 8160 analyzer, (Menarini, Florence, Italy). The HbA1c level was detected by a dual-wavelength colorimetric (415-500) assay. The intra-assay coefficient of variation (CV) was 0.6% at a mean level of 4.9 % and the inter-assay CV 0.8% at a mean level of 5.5%.

Weight and height were measured annually (while people were barefoot and wearing light clothes). *BMI* was calculated by dividing weight (kg) by the square of height (m). Difference in weight was calculated by subtracting the weight at end of follow up from the weight at the start of insulin.

Blood pressure was measured annually. Systolic blood pressure (SBP) was measured three times on the right arm after five minutes of rest in a seated position using a random-zero sphygmomanometer with different oscillometric devices over time. *Fasting glucose levels* were assessed in venous plas-

ma by the glucose-oxidase method (Glucoquant/hexokinase/G6P-DH; Boehringer-Mannheim, Mannheim, Germany). *Triglycerides, total and HDL-cholesterol* were determined from fasting blood samples by enzymatic techniques (Boehringer-Mannheim, Mannheim, Germany).

Microalbuminuria was considered present if UACR > 2.0 mg/mmol. *Retinopathy* (fundus photography of both eyes was performed yearly) was measured from 1998 until 2012, with different Fundus cameras (Kowa Pro Fundus camera, nonmydriatic Canon CR5 camera, nonmydriatic Topcon TRC NW 100 camera) using 45-degree fundus photographs after mydriasis with 0.5% tropicamide and 2.5% phenylephrine eye drops. All photographs were graded by an experienced ophthalmologist according to the EURODIAB classification score [13]. The retinopathy at the end of follow up is calculated for each person at the end of her/ his follow up period.

PCP organisation. Diabetes management differs across PCP practices. Therefore, PCP organisations were categorized into three types: involvement of a nurse practitioner in diabetes management who initiates insulin; involvement of a nurse practitioner and insulin initiation transferred to Diabetes Care System; no nurse practitioner and insulin initiation transferred to Diabetes Care System. Information on medication use was registered yearly at the annual visit by checking the dispensing labels of the medication brought in by people with T2DM.

All measurements were performed at the clinical chemistry laboratory of the Westfries Gasthuis.

Statistical Analysis

HbA1c levels over time

Latent class growth modelling (LCGM) is a type of cluster analysis used to group patients into an optimal number of groups, each with an unique trajectory of HbA1c over time, by modeling heterogeneity in the time course [14,15]. Each class has its own growth parameters (i.e. intercept, slope). To determine the optimal number of classes, a stepwise forward approach was taken, starting with a model with one developmental pattern. Subsequently, one class at a time was added. The optimal model is a model where individuals within a class are most similar to each other and most different to individuals in other classes. The model fit was assessed by the Bayesian Information Criterion (BIC) (where a lower BIC indicates a better fit) and with posterior probabilities (where probabilities > 0.8 are recommended and a probability closer to 1 indicates a better classification) [14]. Also, the usefulness and clinical interpretation of each new derived class was assessed. Usefulness was assessed by considering the number of people in each class (hereby rejecting small classes consisting of less than 1% of the total study population). The final number of classes was based on a low BIC score, good probabilities (> 0.8), and clinically relevant differences between classes.

The number of missing values were small in this study and at random. Missing data at random do not affect model estimates in LGCM.

The demographic characteristics, HbA1c, BMI, SBP, fasting glucose, cholesterol, triglycerides, retinopathy, microalbuminuria, and diabetes duration at baseline were assessed. The mean difference in weight gain for participants in each class was calculated, as well as the percentage of people with oral glucose lowering agents use in addition to insulin, in each class. Finally the percentage of prevalent retinopathy at the end of follow up for each person in each class was assessed.

Differences of the here above described variables between the trajectories were tested with One Way ANOVA and post hoc Bonferroni tests for mean levels, with Chi-square tests for proportions and Kruskal – Wallis test for median levels in the study population.

Subsequently, multivariate logistic backward regression analyses was used to assess which characteristics (e.g. sex, age, HbA1c, BMI, SBP, diabetes duration, triglycerides and cholesterol) at the initiation of insulin were associated with membership of the groups. Group 1 was regarded as reference group.

‘Off-target’ vs. ‘on-target’. To analyse the sustainability of the HbA1c levels over time, the proportion of people with T2DM who were ‘off-target’ and ‘on-target’ was calculated. We defined ‘off-target’ when HbA1c levels were higher than 53 mmol/mol (7.0%) in 1/3 or more of the follow-up time, and ‘on-target’ when HbA1c levels were higher than 53 mmol/mol (7.0%) in less than 1/3 of the follow up time.

Differences of the demographic characteristics, HbA1c, BMI, SBP, fasting glucose, cholesterol, triglycerides, retinopathy, microalbuminuria, metformin use only, SU use only, metformin and SU combination use, other combination use at baseline, and diabetes duration at baseline between the ‘off-target’ group and ‘on-target’ group were tested with One Way ANOVA and post hoc Bonferroni tests for mean levels, with Chi-square tests for proportions and Kruskal – Wallis test for median levels in the study population.

Subsequently, multivariate logistic backward regression analyses was used to assess which person characteristics (e.g. BMI) and disease determinants (e.g. diabetes duration and HbA1c) before the initiation of insulin were associated with membership of the ‘on-target’ group. The ‘off-target’ group was regarded as reference class. All analyses were adjusted for age and sex, in other words sex and age were forced in the multivariable model. All determinants were entered simultane-

ously using the backward elimination method, leading to a model including only significant ($p < 0.05$) determinants.

The proportional hazards assumption, i.e. the constant hazard ratio over time, was evaluated by comparing estimated log-log survival curves for all covariates. All assessed log-log survival plots graphically showed two parallel lines, indicating no violation of the assumption. All continuous variables were divided into quartiles to check whether these variables met the proportional hazard assumption. Data were presented as Odds Ratios (OR) with a 95% confidence interval (CI). P-values lower than 0.05 were considered statistically significant.

The LCGM analyses were conducted with Mplus 7.11. Other statistical analyses were performed with SPSS for Windows (version 20.0, SPSS Inc., Chicago, IL).

RESULTS

Figure 1 shows the disposition of the 1,203 people with T2DM participating in this study, with a mean follow-up of 5.6 year (range 2-10).

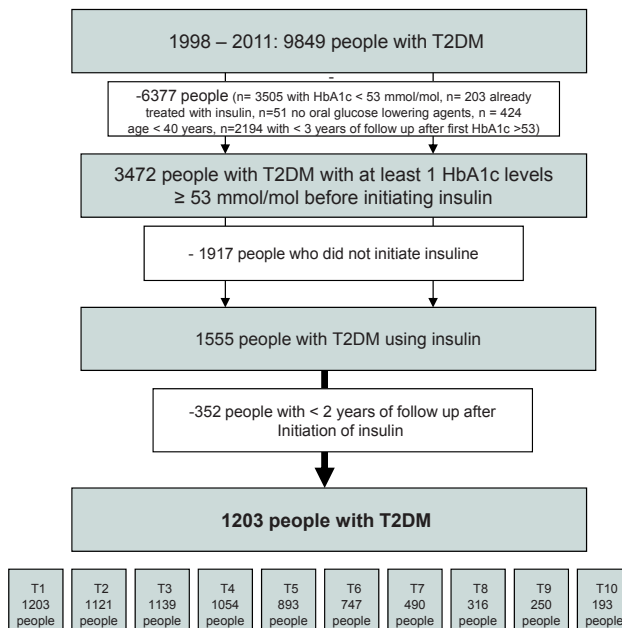


Figure 1. Flowchart of the included people with T2DM.

HbA1c trajectories

LCGM identified four groups of distinct HbA1c trajectories. Figure 2 shows the trajectories of HbA1c over 10 years for the four identified groups after the initiation of insulin. HbA1c levels two years prior to the initiation of insulin were shown as well.

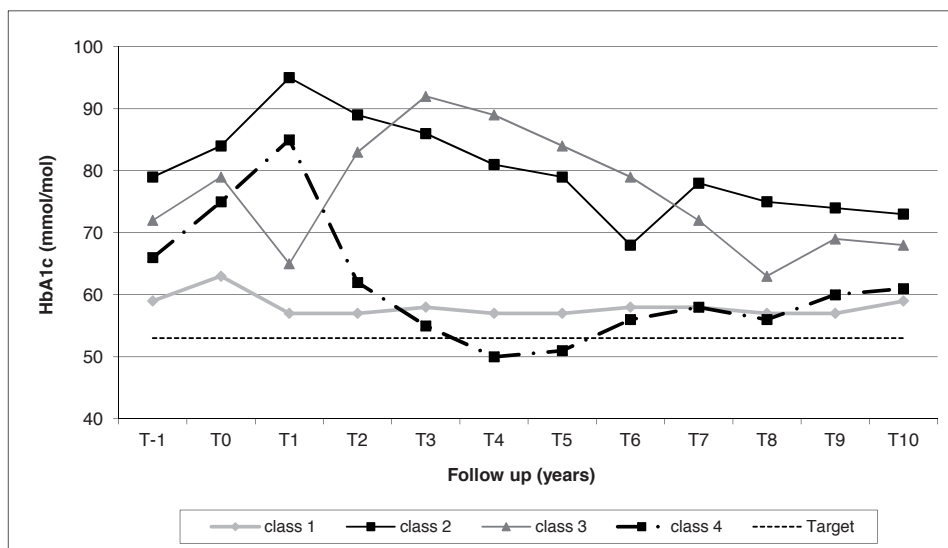


Figure 2. Trajectories of HbA1c over ten years in four groups of people with T2DM after initiation of insulin.

The by far largest group (group 1, $n=1,067$, 88.7%) consisted of people who had stable HbA1c levels during follow up of around 57 mmol/mol (7.4%).

Group 2 ($n=47$, 3.9%) comprised people who had very high HbA1c levels of 95 mmol/mol (10.8%) at initiation of insulin, which thereafter gradually decreased to 73 mmol/mol (8.8%) over a 10 year period.

Group 3 ($n=36$, 3.0%) shows a steadily increasing HbA1c following the initiation of insulin therapy from a baseline level of 65 mmol/mol (8.1%), to 92 mmol/mol (10.6%) at three years.

Group 4 ($n=53$, 4.4%) comprised people who had high HbA1c levels starting at 85 mmol/mol (9.9%) that decreased over the years to around target levels of 51 mmol/mol (6.8%).

Table 1 shows the characteristics of the four groups determined by LCGM analysis. Table 2 shows the results of the multinomial logistic regression analysis. People in group 2, 3 and group 4 had significantly higher baseline levels compared to group 1. People in group 3 were younger com-

Table 1 Baseline characteristics of the people with T2DM in the various groups of HbA1c trajectories following initiation of insulin therapy.

| | Study population | Group 1 | Group 2 | Group 3 | Group 4 |
|--|------------------|------------------|------------------|------------------|------------------|
| N | 1203 | 1067 | 47 | 36 | 53 |
| Baseline | | | | | |
| Age (yr) | 65.4 ± 10.1 | 65.8 ± 9.9 | 59.8 ± 11.4* | 58.6 ± 9.3* | 65.8 ± 11.6 |
| Male (%) | 51.2 | 50.6 | 66.0 | 50.0 | 50.9 |
| Diabetes duration (yr) | 8.3 (5.1 – 12.6) | 8.4 (5.2 – 12.6) | 7.8 (4.5 – 12.6) | 8.2 (4.9 – 13.3) | 8.2 (5.0 – 12.3) |
| HbA1c (mmol/mol (%)) | 60 (7.6) ± 1.3 | 57 (7.4) ± 0.9 | 96 (10.9) ± 1.1* | 65 (8.1) ± 1.0* | 86 (10.0) ± 1.0* |
| BMI (kg/ m ²) | 30.9 ± 5.7 | 30.8 ± 5.7 | 30.3 ± 5.6 | 31.5 ± 6.2 | 31.8 ± 6.1 |
| SBP (mmHg) | 145.3 ± 20.8 | 146.2 ± 20.8 | 135.7 ± 20.2* | 134.0 ± 16.9* | 144.6 ± 19.7 |
| Fasting glucose (mmol/L) | 8.5 ± 2.6 | 8.2 ± 2.2 | 11.9 ± 4.6* | 9.4 ± 3.0* | 11.6 ± 3.4* |
| Total cholesterol (mmol/L) | 4.6 ± 1.1 | 4.6 ± 1.1 | 4.7 ± 1.2 | 4.9 ± 1.1 | 4.7 ± 1.0 |
| HDL cholesterol (mmol/L) | 1.18 ± 0.3 | 1.19 ± 0.3 | 1.09 ± 0.4 | 1.20 ± 0.3 | 1.15 ± 0.3 |
| Triglycerides (mmol/L) | 1.86 ± 1.2 | 1.81 ± 1.1 | 2.16 ± 1.2 | 2.28 ± 1.9 | 2.36 ± 1.4* |
| Metformin use only (%) | 21.9 | 22.3 | 23.4 | 22.2 | 13.2 |
| SU use only (%) | 14.5 | 15.1 | 2.1* | 5.6* | 20.8* |
| Metformin + SU use (%) | 45.1 | 44.8 | 51.1 | 47.2 | 45.3 |
| Other combination use (%) | 4.2 | 4.2 | 4.3 | 5.6 | 1.9 |
| Unknown medication (%) | 14.3 | 13.6 | 19.1 | 19.5 | 18.8 |
| Any Retinopathy (%) | 9.7 | 8.3 | 29.6 | 16.7 | 10.3 |
| Grade 1 Retinopathy (%) | 6.0 | 5.3 | 18.5 | 8.3 | 7.7 |
| Grade 2 Retinopathy (%) | 1.3 | 1.2 | 3.7 | 4.2 | 0 |
| Grade 3 Retinopathy (%) | 0.9 | 0.5 | 3.7 | 8.3 | 2.6 |
| Grade 4 Retinopathy (%) | 1.5 | 1.4 | 3.7 | 4.2 | 0.0 |
| Microalbuminuria (%) | 26.5 | 25.4 | 34.5 | 34.8 | 35.3 |
| Glomerular Filtration Rate (ml/ min/1.73m ²) | 90.3 ± 35.1 | 89.9 ± 34.1 | 104.9 ± 35.3* | 106.1 ± 37.5* | 94.5 ± 47.1 |
| Drop out (%) | 14.5 | 14.1 | 17.0 | 11.1 | 24.5 |
| End of follow up | | | | | |
| Follow up (yr) | 5.6 ± 2.8 | 5.6 ± 2.8 | 6.0 ± 2.8 | 5.9 ± 2.8 | 5.2 ± 2.7 |
| Mortality n (%) | 14.3 | 13.9* | 14.9* | 2.8* | 30.2* |
| Weight differences (kg) | 1.2 ± 6.2 | 1.0 ± 5.8 | 2.1 ± 6.6 | 1.5 ± 9.7 | 2.9 ± 9.7 |

Data represent mean ± standard deviation, proportions, or median (interquartile range). Between-cluster differences were tested with ANOVA and post hoc Bonferroni for mean levels, with χ^2 tests for proportions and Kruskal-Wallis test for median levels. Abbreviation: BMI: body mass index, SBP: systolic blood pressure, SU: sulfonylureas. * statistically significantly ($p < 0.05$) different from class 1.

Table 2 Multivariate regression analyses determining characteristics of different groups, compared to group 1.

| | Model 1 | Model 2 |
|-------------------------------|------------------------|--------------------------|
| Group 2 versus Group 1 | | |
| Male | 0.81 (0.25 to 2.57) | |
| Age (yr) | 0.97 (0.92 to 1.03) | 0.96 (0.91 to 1.01) |
| HbA1c (mmol/mol) | 41.60 (17.93 to 96.70) | 47.56 (20.84 to 108.56)* |
| Glucose (mmol/L) | 1.03 (0.87 to 1.23) | |
| SBP (mmHg) | 0.99 (0.96 to 1.02) | |
| Triglycerides (mmol/L) | 1.35 (0.90 to 2.05) | |
| Group 3 versus Group 1 | | |
| Male | 1.11 (0.51 to 2.46) | |
| Age (yr) | 0.95 (0.91 to 0.99)* | 0.93 (0.89 to 0.97)* |
| HbA1c (mmol/mol) | 1.81 (1.16 to 2.84)* | 2.08 (1.41 to 3.07)* |
| Glucose (mmol/L) | 1.09 (0.93 to 1.29) | |
| SBP (mmHg) | 0.97 (0.95 to 0.99)* | |
| Triglycerides (mmol/L) | 1.20 (0.97 to 1.49) | |
| Group 4 versus Group 1 | | |
| Male | 0.78 (0.31 to 1.97) | |
| Age (yr) | 1.01 (0.97 to 1.06) | 1.01 (0.97 to 1.05) |
| HbA1c (mmol/mol) | 18.18 (9.03 to 36.59)* | 20.86 (10.46 to 41.60)* |
| Glucose (mmol/L) | 1.05 (0.90 to 1.23) | |
| SBP (mmHg) | 1.00 (0.98 to 1.02) | |
| Triglycerides (mmol/L) | 1.33 (0.99 to 1.78) | |

Estimates are odds ratios with 95% confidence intervals. A * indicates a significant association ($P < 0.05$). Model 1 shows the multivariate model including determinants with p -values < 0.10 . Model 2 shows the final model after backward selection, including variables with p -values < 0.05 . Nagelkerke R square is 0.61

pared to group 1. People in group 4 were using significantly more SU only compared to the other groups (20.8% vs. 15.1%, 2.1% and 5.6%). The total mortality in group 4 was significantly higher compared to the other groups (30.2% vs. 13.9%, 14.9% and 2.8%, $p = 0.002$).

‘Off-target’ vs. ‘on-target’

Of the 1,203 people initiating insulin therapy 294 people (24.4%) were ‘on-target’, whereas 909 people (75.6%) were ‘off-target’ with an equal follow-up of 5.5 year. People in the ‘off-target’ group were significantly younger, and had higher HbA1c and glucose levels at the initiation of insulin. More people in the ‘off-target’ group were using a combination of metformin and sulfonylureas (Table 3). There was no difference in total mortality between ‘off-target’ (14.0%) and ‘on-target’ (16.0%).

Table 3 Baseline characteristics of the people in the 'off-target' group and 'on-target' group.

| | On-target | Off-target |
|---|------------------|-----------------|
| N (%) | 294 (24.4) | 909 (75.6) |
| Baseline | | |
| Age (yr) | 67.3 ± 9.9* | 64.8 ± 10.1* |
| Male (%) | 52.4 | 50.8 |
| Diabetes duration (yr) | 8.2 (4.8 – 12.9) | 8.4 (5.3– 12.4) |
| HbA1c (mmol/mol) (%) | 50 (6.7) ± 0.8* | 63 (8.0) ± 1.2* |
| BMI (kg/ m ²) | 31.0 ± 6.2 | 30.8 ± 5.6 |
| SBP (mmHg) | 146.9 ± 21.1 | 144.9 ± 20.7 |
| Fasting glucose (mmol/L) | 7.5 ± 2.1* | 8.8 ± 2.7* |
| Total cholesterol (mmol/L) | 4.6 ± 1.0 | 4.6 ± 1.1 |
| HDL cholesterol (mmol/L) | 1.20 ± 0.3 | 1.17 ± 0.3 |
| Triglycerides (mmol/L) | 1.88 ± 1.5 | 1.86 ± 1.1 |
| Metformin use only (%) | 22.8 | 21.7 |
| SU use only(%) | 15.3 | 14.3 |
| Metformin + SU use (%) | 40.5* | 46.6* |
| Other Combination use (%) | 6.1* | 3.5* |
| Unknown medication use (%) | 15.3 | 13.9 |
| Any Retinopathy (%) | 6.8 | 10.6 |
| Grade 1 Retinopathy (%) | 3.4 | 6.8 |
| Grade 2 Retinopathy (%) | 0 | 1.7 |
| Grade 3 Retinopathy (%) | 1.1 | 0.9 |
| Grade 4 Retinopathy (%) | 2.3 | 1.2 |
| Microalbuminuria (%) | 24.0 | 27.3 |
| Glomerular Filtration Rate (ml/min/1.73m ²) | 84.7 ± 33.0 | 89.6 ± 33.5* |
| Follow-up duration (yr) | 5.4 | 5.5 |
| Total mortality (%) | 16.0 | 14.0 |

Data represent mean ± standard deviation, proportions, or median (interquartile range). Between-cluster differences were tested with ANOVA and post hoc Bonferroni for mean levels, with χ^2 tests for proportions and Kruskal-Wallis test for median levels. Abbreviation: BMI: body mass index, SBP: systolic blood pressure, SU: sulfonylureas. * statistically significantly ($p < 0.05$) different.

Table 4 shows which characteristics were associated with the membership of the 'on-target' group compared to the 'off-target' group. People within the 'on-target' group had statistically significant lower HbA1c levels before the initiation of insulin (OR 0.69, 95% CI 0.62 to 0.78).

Table 4 Main identified determinants of ‘on-target’ versus ‘off-target’ to insulin therapy.

| | Univariate OR (95% CI) | Multivariable OR (95% CI) |
|---------------------------|------------------------|---------------------------|
| Sex (female) | 0.94 (0.72 – 1.22) | 0.85 (0.65 – 1.12) |
| Age (years) | 1.03 (1.01 – 1.04)* | 1.02 (1.01 – 1.04)* |
| HbA1c (mmol/mol) | 0.68 (0.61 – 0.76)* | 0.69 (0.62 – 0.78)* |
| BMI (kg/ m ²) | 1.01 (0.99 – 1.04) | |
| Diabetes duration | 1.00 (0.98 – 1.02) | |

Estimates are odds ratio's with 95% confidence intervals. A * indicates a significant association ($P<0.05$). Model 1 shows univariate associations with class membership. Model 2 shows the final model after backward selection.

Figure 3 shows the percentage of people ‘on-target’ to insulin therapy in accord to the HbA1c level before the initiation of insulin.

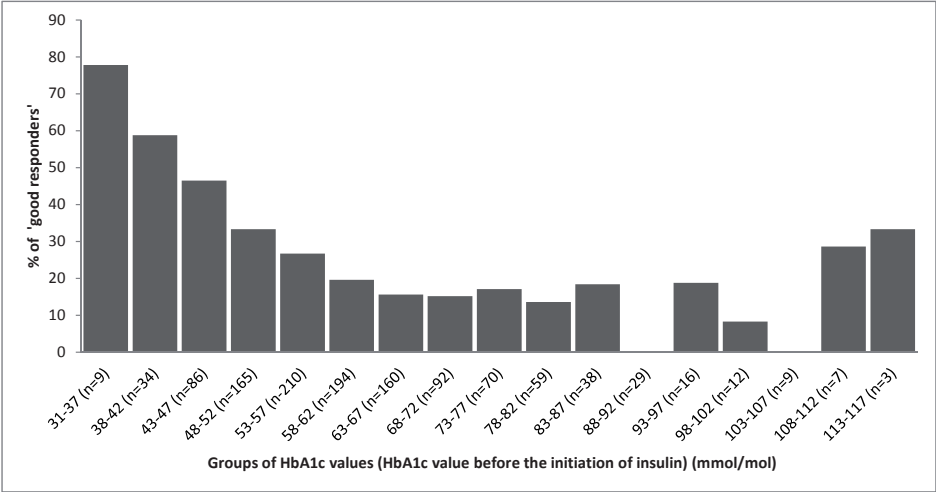


Figure 3. Percentage of people ‘on-target’ to insulin therapy in accord to the HbA1c value before initiation of insulin.

DISCUSSION

Four distinct trajectories of HbA1c were identified with Latent Class Growth Modelling (LCGM) in people with T2DM initiating insulin. Only 24.4% of the people showed a ‘good response’ to insulin during follow up. These were the older people with a lower HbA1c level at the start of insulin treatment.

A previous study, in agreement with our finding, showed that a lower HbA1c at the start of insulin treatment was associated with a higher likelihood of reaching the ‘on-target’ group [8,16-19]. However, the previous studies were shorter (up to 1 year), and the defined target did not include

sustained glycemic control. In the United Kingdom Prospective Diabetes Study (UKPDS) study, patients in the intensive treatment group (treated with insulin) reached a median HbA1c level of 53 mmol/mol (7.0%) over 10 years [20]. However, the baseline HbA1c values of the 911 patients initiating insulin in the UKPDS study were much lower compared to those in our study (43 mmol/mol (6.0%) in the UKPDS vs. 63 mmol/mol (8.0%) in this study) and in contrast to our study the UKPDS included newly diagnosed people with T2DM [20].

A considerable number of people (n=294) with T2DM were in good control in the year prior to initiation of insulin therapy. The reason for initiation insulin in these people is not clear. PCPs may have based their decision to initiate insulin on more HbA1c measurements and on other not defined reasons. It is also imaginable that people with T2DM were experiencing side effects of oral glucose lowering agents, and were prepared and mentally ready to start insulin therapy.

Taken together, these data strongly suggest that initiating insulin earlier increases the likelihood of achieving and sustaining glycemic control [21-23]. Early intensive insulin therapy has been shown to improve β cell function with long lasting beneficial effect on glycemic control [23,24]. The obvious risk of the availability of multiple oral agents is that insulin therapy will be unduly delayed in people with poor glycemic control [25,26].

The percentage of mortality in group 4 was higher compared to the other groups, despite comparable baseline parameters. The higher mortality rate could be explained by the higher rate of glucose lowering in this group and subsequently the risk of hypoglycaemia. This is in concordance with the results from the ACCORD study, the Veterans Affairs Trial as well as the General Practice Research Database [27-29]. It is interesting to note that people in class 2 also had poor HbA1c levels at baseline, but the reduction in HbA1c during follow up was less rapid and not associated with excess mortality.

There are some limitations to consider. This study was performed in a centrally organised managed diabetes care system, in which a strict treatment algorithm [30] was applied by all caregivers in this region. Therefore, this cohort is by no means representative for diabetes care in other regions. However, this cohort provided the optimal circumstance to address the current study question. It will be of great interest to perform a similar analysis in a different treatment setting. The identified determinants of successfully achieving glycemic control corroborate earlier findings and were probably not impacted by this study cohort [17,18]. Other limitations were that insulin doses and adherence to the insulin titration algorithm were not collected. Finally, we don't have information on co-morbidities.

The use of LCGM as a method to define groups with distinct trajectories has some limitations. The first limitation concerns the complexity and flexibility of the model and each decision could influence the final number of classes. Furthermore, LCGM can lead to an imbalance in the number of subjects in each trajectory. As a result of this, extraction of the classes is a simplification of the reality and is not necessarily reflect the true existence of multiple subgroups [14]. However, strength of LCGM is that categorisation is not based on a-priori determined subgroups, but they are based on trajectory characteristics of HbA1c within the data. Further, LCGM is focused on relationships among individuals, and creates the condition to categorise them in homogenous subgroups. To our knowledge, this is the first population based observational T2DM cohort study using LCGM to define trajectories of HbA1c in patients initiating insulin. Other strengths of this study are the completeness of the measurements, the long follow up after the initiation of insulin, information on HbA1c levels before the initiation of insulin, the standardized yearly measurements, our definition of 'on-target' and 'off-target', which is simple and easy to replicate in other T2DM populations but were not described before.

In summary, our study showed four distinct groups of HbA1c trajectories in people with T2DM initiating insulin therapy. Lower HbA1c at baseline was associated with better glycemic response to insulin. Initiating insulin earlier in the course of T2DM, when HbA1c levels are only modestly elevated, increases the probability of achieving and sustaining target glycemic values.

The 'on-target' group may represent a subgroup with a less progressive disease. However, the group with a rapidly lowering HbA1c after insulin initiation had a higher mortality. This might implicate that less strict glucose lowering is desirable in some categories of people with T2DM, and 'personalised care' is necessary.

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Chapter 4

Distinct HbA1c trajectories in a Type 2 Diabetes cohort.

Iris Walraven, Ruth Mast, Trynke Hoekstra, AP Danielle Jansen, Amber AWA van der Heijden, Simone P Rauh, Femke Rutters, Esther van't Riet, Petra JM Elders, Annette C Moll, Betina CP Polak, Jacqueline M Dekker, Giel Nijpels.

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ABSTRACT

Background To identify subgroups of people with type 2 diabetes mellitus (T2DM) with distinct HbA1c trajectories. Subgroup characteristics were determined and the prevalence of microvascular complications over time was investigated.

Research Design and Methods Data from a cohort of 5,423 people with T2DM from a managed primary care system was used (mean follow-up 5.7 years (range 2-9 years)). Latent Class Growth Modeling (LCGM) was used to identify subgroups of people with distinct HbA1c trajectories. Multinomial logistic regression analyses were conducted to determine which characteristics were associated with different classes.

Results Four subgroups were identified. The first and largest subgroup (83%) maintained good glycemic control over time ($\text{HbA1c} \leq 53 \text{ mmol/mol}$), the second subgroup (8%) initially showed severe hyperglycemia, but reached the recommended HbA1c target within two years. Persons within this subgroup had significantly higher baseline HbA1c levels but were otherwise similar to the good glycemic control group. The third subgroup (5%) showed hyperglycemia and a delayed response without reaching the recommended HbA1c target. The fourth subgroup (3.0%) showed deteriorating hyperglycemia over time. Persons within the last two subgroups were significantly younger, had higher HbA1c levels and a longer diabetes duration at baseline. These subgroups also showed a higher prevalence of retinopathy and microalbuminuria.

Conclusions Four subgroups with distinct HbA1c trajectories were identified. More than 90% reached and maintained good glycemic control (subgroup one and two). People with T2DM within the two subgroups that showed a more unfavorable course of glycemic control, were younger, had higher HbA1c levels and a longer diabetes duration at baseline.

INTRODUCTION

Strict glycemic control is essential in managing people with type 2 diabetes mellitus (T2DM). The risk of developing both micro- and macrovascular complications increases considerably as glycated hemoglobin A1c levels (HbA1c) rise [1-3]. Furthermore, long-term cumulative effects of hyperglycemia are known to be associated with an increased risk of all-cause and cardiovascular mortality [4,5].

The current ADA/EASD guidelines [6] for the management of T2DM recommend HbA1c levels of ≤ 53 mmol/mol ($\leq 7.0\%$) in patients with early T2DM or a relatively long life expectancy. Although most patients respond adequately to glucose-lowering therapy [7], T2DM has a heterogeneous character. Not every patient may benefit from the same type of glucose management and there may be certain patients for whom different care strategies and less stringent HbA1c targets are appropriate. Therefore, the current ADA/EASD guidelines [6] also placed emphasis on a more personalized care approach where higher HbA1c goals are accepted in patients not likely to reach an HbA1c ≤ 53 mmol/mol ($\leq 7.0\%$).

These guidelines were merely based on outcomes of randomized clinical trials (RCTs) [6]. However, patients included in RCTs do not reflect the general T2DM population and represent only a highly selected patient group defined with detailed in- and exclusion criteria. Long-term clinical data derived from patients who were treated within regular diabetes care are scarce. As a consequence, clinical characteristics of people with T2DM with glycemic control trajectories that are distinct from achieving the recommended HbA1c target are inadequately studied. Latent class growth modelling (LCGM) is an innovative statistical method used to determine those subgroups (classes) of patients with distinct HbA1c trajectories [8]. Identifying those classes may help to characterize patients for whom personalized care strategies are needed to reach a more 'tailor made' HbA1c target.

The Diabetes Care System (DCS) West-Friesland in The Netherlands consists of a large primary care cohort of people with T2DM. The DCS has a long-term and well-characterized follow-up and offers the opportunity to identify classes of glycemic control trajectories, which is the primary aim of this study. Second, we assessed which characteristics are associated with membership in identified classes and whether different classes are associated with varying risks of developing microvascular complications.

RESEARCH DESIGN AND METHODS

An observational cohort study was performed with data from the Diabetes Care System (DCS) West-Friesland, described in detail elsewhere [9]. In short, the DCS organizes managed diabetes

care with contracted health care providers in the region of West-Friesland in The Netherlands, a region with about 200,000 inhabitants, representative of a Caucasian population. All general practitioners in the region refer a patient to the DCS as soon as he/she is diagnosed with T2DM.

Study population

In the period between 1998 and 2011, 9,849 people with T2D with varying diabetes durations entered the DCS in different years. For each patient, the year of entry to the DCS was considered to be the baseline measurement (T1). Due to the open and dynamic nature of the cohort, the number of patients decreased every year due to loss to follow-up, referral or death. In addition, 'newer' patients who entered the cohort at a later stage, had a shorter follow-up duration.

Figure 1 presents a flowchart of the included study population. To be able to perform latent class growth modelling, all people with T2DM ($n = 5,423$) with a minimum follow-up of two years were selected. Patients that were excluded because they had less than two years of follow-up ($n=4,426$) had a significantly lower HbA1c (-0.1%), lower BMI (-0.31 kg/m^2), lower total cholesterol (-0.3 mmol/L), higher age ($+5.3 \text{ years}$), higher systolic blood pressure ($+3.2 \text{ mmHg}$) and a lower diastolic blood pressure (-2.2 mmHg) at baseline.

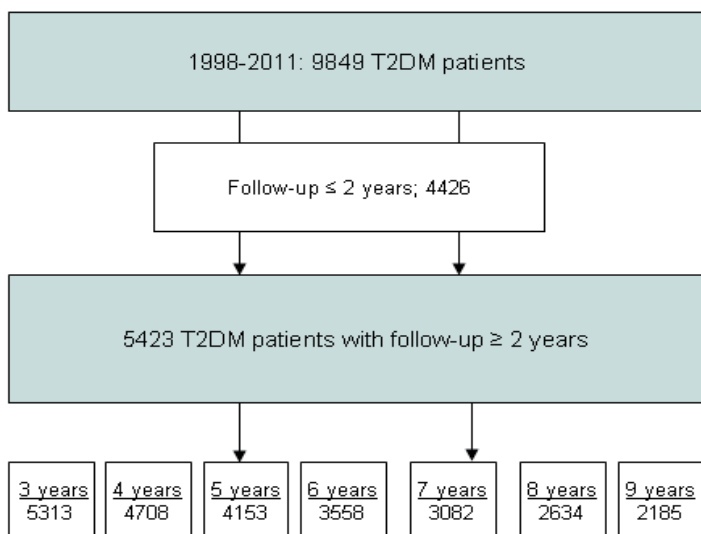


Figure 1. Flowchart of included patients within the DCS.

Confirmation of diabetes Year of onset of diabetes was obtained by self-report. Furthermore, T2DM was considered confirmed if at least one of the following criteria was present: 1) one or more classic symptoms (excessive thirst, polyuria, weight loss, hunger or pruritus) and (fasting plasma glucose ≥ 7.0 mmol/l or random plasma glucose ≥ 11.1 mmol/l); 2) at least two elevated plasma glucose levels on different occasions (fasting glucose ≥ 7.0 mmol/l or random plasma glucose ≥ 11.1 mmol/l) [10]. The presence of the above mentioned criteria was investigated by the GP and was most of the times regarded as the year of onset of diabetes. When the confirmation of diabetes and self-reported year of onset of diabetes differed, the reason for the difference was investigated.

Drop-outs were identified as those lost to follow-up due to death, referral and migration.

HbA1c level was assessed yearly with a DCCT standardized reversed-phase cation exchange chromatography (HA 8160 analyzer, Menarini, Florence, Italy). The HbA1c level was detected by a dual-wavelength colorimetric (415-500). The intra-assay coefficient of variation (CV) was 0.6% at a mean level of 4.9% and the inter-assay CV was 0.8 % at a mean level of 5.5%.

Measurements

Fasting glucose was measured yearly in venous plasma by the glucose-oxidase method (Glucoquant/hexokinase/G6P-DH; Boehringer-Mannheim, Mannheim, Germany). *Weight and height* were measured yearly (while patients were barefoot and wearing light clothing). *BMI* was calculated by weight in kilograms divided by the height in meters squared.

Systolic and diastolic blood pressure were measured three times on the right arm after five minutes of rest in a seated position, using a random-zero sphygmomanometer (Hawksley-Gelman, Lancing, Sussex, UK); from 2003 on, an oscillometric device was used (Colin Press-Mate BP-8800, Komaki City, Japan; from 2009 on, Welch Allyn ProBP 3400, Skaneateles Falls, NY, USA). *Total cholesterol* level was measured using enzymatic techniques (Boehringer Mannheim, Mannheim, Germany).

Current medication use Use of metformin, sulfonylureas (SU) derivatives and insulin was obtained by yearly self-report. Information on medication use was compared with data from the PHARMO Network, which is a comprehensive record linkage system in which drug dispensing data in a regional/national catchment area are linked to a registry of hospital discharge diagnoses and other registries.

Microvascular complications

Urinary albumin-creatinin ratio (UACR) in mg/mmol was determined yearly in an overnight, first-voided urine sample. Urinary albumin was measured by rate nephelometry (Array Protein

System; Beckman Coulter, Fullerton, CA) with an assay threshold of 2 mg/L. Urinary creatinin was measured using a modified Jaffé test. *Microalbuminuria* was considered present if UACR > 2.0 mg/mmol. *Retinopathy* From 1998 until 2000, fundus photography of both eyes was performed yearly with a Kowa Pro Fundus camera with a green filter (Kowa Optical Industry, Torrance, CA). Black and white, 35-mm photographs were taken 30 min after mydriasis with 0.5% tropicamide and 2.5% phenylephrine eye drops. From the beginning of 2000 until 2004, fundus photography of both eyes was performed with a nonmydriatic Canon CR5 camera (Canon Inc., Tokyo, Japan). From 2004, fundus photography of both eyes was performed using a nonmydriatic Topcon TRC NW 100 camera (Topcon, Tokyo, Japan) (9). All participants were examined using 45-degree fundus photographs. One photograph was centred on the macula and the other nasally with one optic disc diameter from the temporal side. All photographs were graded by an experienced ophthalmologist according to the EURODIAB classification score [11], in which grade 0 is “no retinopathy,” grade 1 is “minimal nonproliferative retinopathy,” grade 2 is “moderate nonproliferative retinopathy,” grade 3 is “severe nonproliferative or preproliferative retinopathy,” grade 4 is “photocoagulated retinopathy,” and grade 5 is “proliferative retinopathy.” In the DCS, EURODIAB grades 4 and 5 were combined and considered to be grade 4.

Statistical analysis

Baseline characteristics are presented as proportion, mean (\pm SD) or median (interquartile range) in the case of a skewed distribution.

Latent Class Growth Modeling (LCGM) was used to identify classes of people with T2DM with distinct trajectories of HbA1c over time [8]. LCGM is a type of cluster analysis used to group patients into an optimal number of classes, each with a unique trajectory of HbA1c over time, by modeling heterogeneity over the course of time. To determine the optimal number of classes, the stepwise forward approach was taken starting with a model with one developmental pattern. Then, one class at a time was added. The model fit was assessed with posterior probabilities (where probabilities > 0.8 are recommended and a probability closer to 1 indicates a better classification) and by the Bayesian Information Criterion (BIC) (where a lower BIC indicates a better fit). The BIC considers the likelihood of the model as well as the number of parameters in the model. A lower BIC implies a better fit of the model, where a difference of at least 10 points is regarded as a sufficient improvement [8]

The final number of classes was based on a low BIC score, good probabilities (> 0.8) and clinically relevant differences between classes.

Baseline characteristics of classes were assessed and differences (mean (\pm SD), proportion or median in the case of skewed distribution) were tested using ANOVA (continuous variables), Chi-square tests (categorical variables). Overall p-values for between group differences are reported.

Subsequently, a model was created using multinomial logistic backward regression analysis. In this analysis, we assessed which available patient and disease determinants at baseline were associated with membership in classes different than the reference class. The glycemic control class that reached the recommended HbA1c target (≤ 53 mmol/mol) was regarded as the reference class. In the first step, all potential determinants of membership (all determinants that were available, those included in our baseline table) were analyzed separately and co-linearity was tested by assessing correlations. Linearity of the relationship between determinants and the outcome was tested with the Hosmer & Lemeshow-test. In the second step, all determinants with p-values < 0.10 were entered simultaneously using the backward elimination method, leading to a model that included only significant ($p < 0.05$) determinants.

Associations of class membership with development of retinopathy (EURODIAB grade 1 to 5), microalbuminuria and medication use during follow-up were examined by constructing plots and graphically comparing differences between classes. Statistical significant differences were tested using a binomial mixed modeling approach, accounting for both individual and time levels.

Sensitivity analyses In 2006, new Dutch guidelines for the management of T2DM were adopted and glycemic targets were lowered from HbA1c levels of 60 mmol/mol to 53 mmol/mol [12]. To investigate whether time-dependent trajectories due to guideline alterations were present, sensitivity analyses were performed by conducting LCGM analyses in a subsample of the cohort, i.e. in those who entered the DCS before 2006.

Second, people with T2DM in our cohort had varying diabetes durations at baseline. To investigate whether diabetes duration at baseline influenced the construction of classes in our cohort, we further conducted LCGM analyses in a subsample of newly diagnosed T2DM patients (diabetes duration \leq one year, $n=2,861$).

The LCGM analyses were conducted with Mplus 5.21, MLwin 2.25 was used to conduct binomial mixed modeling and further analyses were performed with SPSS 20.0.

RESULTS

Baseline characteristics. Table 1 presents baseline characteristics of the cohort and of classes identified with LCGM. 5,423 people with T2DM (mean age 61 years, 53% male, mean HbA1c level 58 mmol/mol) with a mean follow-up duration of 5.7 years (range two to nine years) were included.

Table 1. Baseline characteristics according to different classes of HbA1c

| | Cohort | Good glycemic control | Fast responders | Insufficient glycemic control | Bad responders | Overall P-value |
|---|----------------|-----------------------|-----------------|-------------------------------|-----------------|-----------------|
| N (%) | 5423 (100) | 4508 (83.1) | 444 (8.2) | 284 (5.2) | 187 (3.4) | - |
| Entry (yr) | 2003 (3.5) | 2004 (3.5) | 2003 (2.9) | 2002 (3.2) | 2002 (3.0) | <0.001 |
| Drop-out (%) | 522 (9.6) | 416 (9.2) | 53 (11.9) | 33 (11.6) | 20 (10.7) | 0.101 |
| Follow-up (yr) | 5.7 (2.3) | 5.6 (2.3) | 6.9 (2.3) | 6.0 (2.4) | 7.1 (1.6) | <0.001 |
| Sex (% male) | 2902 (53.3) | 2355 (52.2) | 268 (60.4) | 162 (60.4) | 117 (62.6) | <0.001 |
| Age (yr) | 60.6 (11.6) | 61.2 (11.3) | 58.9 (12.3) | 56.9 (11.7) | 55.4 (13.9) | <0.001 |
| Diabetes duration (yr) | 1.0(0.2-3.6) | 1.0(0.2-3.3) | 0.3 (0.1-1.3) | 4.1 (0.9-8.8) | 1.4 (0.3-5.7) | <0.001 |
| HbA1c (mmol/mol) | 57.8 (19.7) | 52.3 (13.9) | 98.7 (15.1) | 75.7 (18.0) | 62.9 (17.5) | <0.001 |
| Fasting glucose (mmol/L) | 8.6 (3.2) | 8.1 (3.0) | 11.7 (3.5) | 10.8 (3.4) | 9.3 (2.7) | <0.001 |
| BMI (kg/m ²) | 30.1 (5.4) | 29.9 (5.2) | 29.6 (5.6) | 31.6 (6.9) | 31.1 (5.0) | <0.01 |
| SBP (mmHg) | 142.8 (20.9) | 143.3 (20.6) | 140.3 (20.8) | 140.3 (22.4) | 140.8 (23.1) | 0.114 |
| DBP (mmHg) | 81.4 (11.0) | 81.1 (10.1) | 82.3 (11.0) | 82.8 (11.6) | 82.9 (11.0) | <0.01 |
| Hdl cholesterol (mmol/L) | 1.2 (0.3) | 1.2 (0.3) | 1.2 (0.3) | 1.2 (0.3) | 1.2 (0.3) | <0.01 |
| Total cholesterol (mmol/L) | 5.3 (1.2) | 5.2 (1.2) | 5.6 (1.4) | 5.6 (1.2) | 5.3 (1.2) | 0.052 |
| Prevalence of complications at baseline | | | | | | |
| UACR | 0.7(0.4 - 1.5) | 0.7 (0.4 - 1.4) | 1.0 (0.5 - 2.4) | 1.0 (0.5 - 2.7) | 0.8 (0.5 - 1.7) | <0.001 |
| Microalbuminuria (%) | 1102 (20.3) | 834 (18.5) | 134 (30.2) | 89 (31.3) | 45 (24.0) | <0.001 |
| Any retinopathy (%) | 429 (8.6) | 309 (7.5) | 46 (10.6) | 49 (18.7) | 25 (14.7) | <0.001 |
| Diabetes medication at baseline | | | | | | |
| Metformin use (%) | 2548 (47.0) | 2028 (45.0) | 284 (64.0) | 139 (48.9) | 97 (51.9) | <0.001 |
| SU use (%) | 2406 (44.4) | 1965 (43.6) | 213 (48.0) | 134 (47.2) | 94 (50.3) | 0.172 |
| Insulin use (%) | 473 (8.7) | 319 (7.1) | 44 (10.0) | 83 (29.2) | 27 (14.4) | <0.001 |

*Mean (SD) or median + interquartile range in the case of skewed distribution * statistically significantly ($p < 0.05$) different from the good glycemic control class. Abbreviations; yr: year, BMI: Body Mass Index; UACR: urinary albumin-to-creatinin ratio, SU: sulfonylureas.*

Four classes with distinct trajectories of HbA1c levels were identified (Figure 2). A four-class solution was found to be the best model according to the criteria described in the statistical analysis section. From class 1, the BIC continued to decrease more than 10 points with the addition of

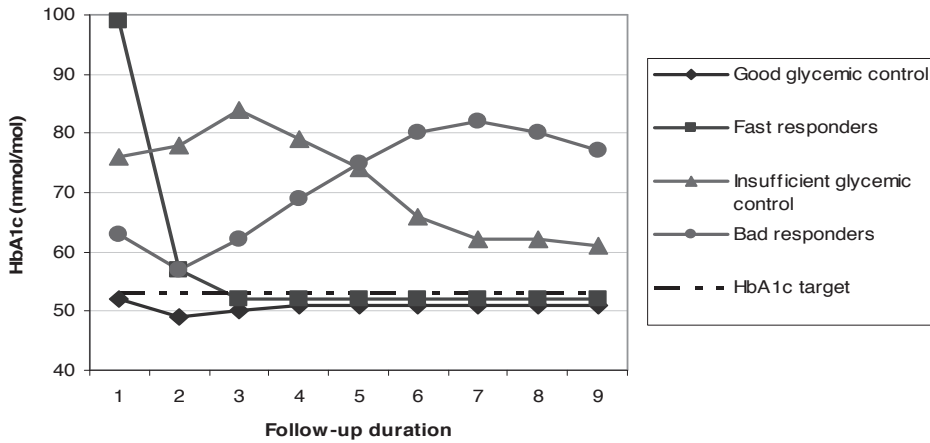


Figure 2. Trajectories of HbA1c according to different classes identified by LCGM.

each class (98486, 97146, 96590, 96142 and 95864, respectively). Until the fifth class, posterior probabilities remained above 0.80. The addition of a fifth class lowered the posterior probabilities in one class below 0.80 and did not result in identification of a useful class for clinical practice.

The largest class (83.1% of the patients were classified in this group) showed a stable pattern of good glycemic control (HbA1c level ≤ 53 mmol/mol) over time and was therefore named the good glycemic control class, the second class (8.2%) initially showed severe hyperglycemia (mean HbA1c level 99 mmol/mol), then adequately responded to glucose management and reached the target HbA1c level of ≤ 53 mmol/mol within two years of follow-up. For the purposes of the current study, this class was named the fast responders class. The third class (5.2%) initially showed hyperglycemia (mean HbA1c level 76 mmol/mol) during the first three years, showed insufficient response to glucose management and did not reach the recommended HbA1c target and was therefore named the insufficient glycemic control class. The fourth class (3.4%) did not respond to glucose management and showed deteriorating hyperglycemia during follow-up and was therefore named the bad responders class (Figure 2).

Compared to the good glycemic control class, classes two to four were significantly younger, had a longer duration of diabetes (with the exception of the fast responders class, that had a shorter duration of diabetes) and more patients entered the DCS during the earlier years of the study (Table 1). Drop-out rates did not differ across the different classes.

Determinants of identified classes Table 2 shows the results of the multinomial logistic regression analysis. Patients within the fast responders class had significantly higher baseline

Table 2. Multivariate regression analyses determining characteristics of different classes, compared to class 1 (good glycemic control).

| | Model 1 | Model 2 |
|---|---------------------------|---------------------------|
| Class 2 (fast responders) versus class 1 | | |
| Sexe (female vs. male) | 0.76 (0.51 - 1.11) | |
| HbA1c (mmol/mol) | 6.60 (5.60 - 7.76) | 6.41 (5.64 - 7.29) |
| Diabetes duration (yr) | 0.98 (0.89 - 1.09) | |
| Age (yr) | 1.02 (1.01 - 1.04) | |
| Total cholesterol (mmol/L) | 1.12 (0.96 - 1.30) | |
| BMI (kg/m ²) | 1.04 (1.00 - 1.04) | |
| Class 3 (insufficient glycemic control) versus class 1 | | |
| Sexe (female vs. male) | 0.75 (0.55 - 1.03) | |
| HbA1c (mmol/mol) | 2.86 (2.55 - 3.20) | 2.88 (2.61 - 3.17) |
| Diabetes duration (yr) | 1.61 (1.45 - 1.79) | 1.54 (1.41 - 1.68) |
| Age (yr) | 0.98 (0.96 - 0.99) | 0.98 (0.96 - 0.99) |
| Total cholesterol (mmol/L) | 1.15 (1.01 - 1.31) | |
| BMI (kg/m ²) | 1.06 (1.03 - 1.09) | 1.06 (1.03 - 1.08) |
| Class 4 (bad responders) versus class 1 | | |
| Sexe (female vs. male) | 0.64 (0.45 - 0.91) | |
| HbA1c (mmol/mol) | 1.59 (1.41 - 1.79) | 1.70 (1.53 - 1.89) |
| Diabetes duration (yr) | 1.20 (1.08 - 1.33) | 1.21 (1.11 - 1.33) |
| Age (yr) | 0.97 (0.95 - 0.98) | 0.96 (0.95 - 0.98) |
| Total cholesterol (mmol/L) | 1.12 (0.97 - 1.30) | |
| BMI (kg/m ²) | 1.03 (1.00 - 1.07) | |

Estimates are odds ratios with 95% confidence intervals. A * indicates a significant association ($P < 0.05$). Model 1 shows the multivariate model including determinants with p -values < 0.10 . Model 2 shows the final model after backward selection, including variables with p -values < 0.05 . Nagelkerke R square is 0.56.

HbA1c levels, but were otherwise similar to the good glycemic control class. Patients within the insufficient glycemic control class and the bad responders class had significantly higher baseline HbA1c levels, a longer duration of diabetes and were younger. Patients within the insufficient glycemic control class further had significantly higher BMI levels as compared to patients with good glycemic control.

Microvascular complications Figure 3 shows the presence of microvascular complications (retinopathy and microalbuminuria) over time, stratified for the different classes. Retinopathy and microalbuminuria over time were statistically significant more prevalent in classes two to four, compared to the good glycemic control class. The bad responders class showed an increasing prevalence of microalbuminuria over time, while other classes either showed a stable or diminishing prevalence over time.

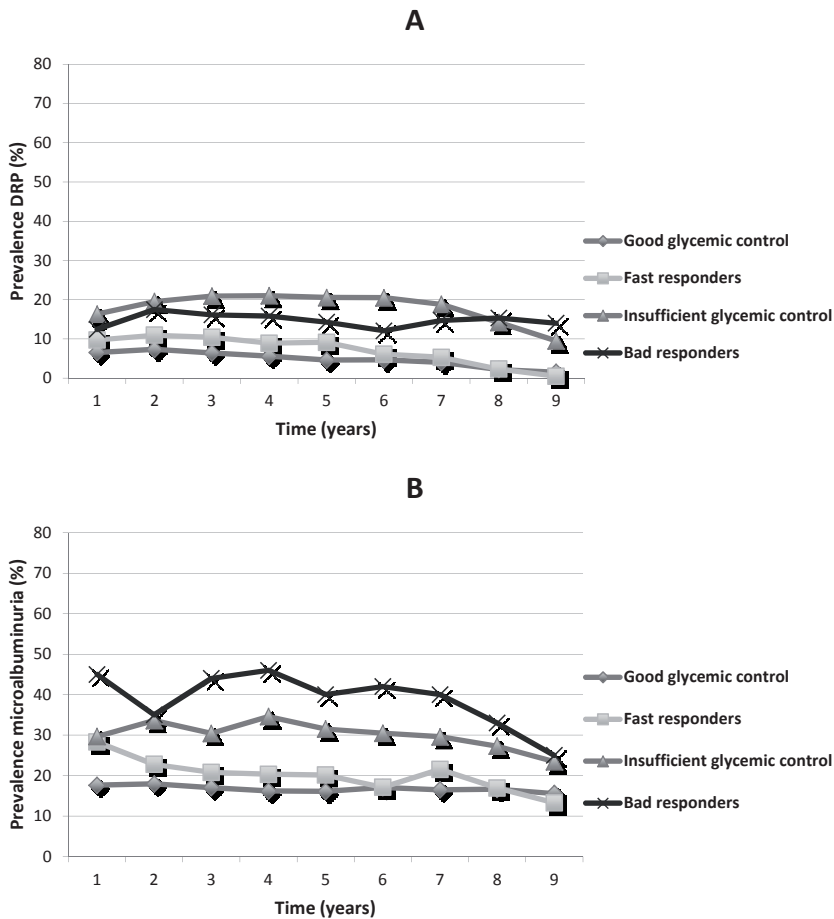


Figure 3. Prevalence of retinopathy (A) and microalbuminuria (>2.0 mg/mmol) (B) according to different classes of HbA1c.

Medication use Figure 4 shows the medication trajectories of the different classes of glycemic control during follow-up. Use of any diabetes medication increased over time in all classes. Patients within the good glycemic control and the fast responders class mainly used metformin and SU-derivates and had the lowest utilization of insulin over time. The insufficient glycemic control class and the bad responders class had a similar pattern of medication use and in both groups 80% of the patients used insulin at nine years.

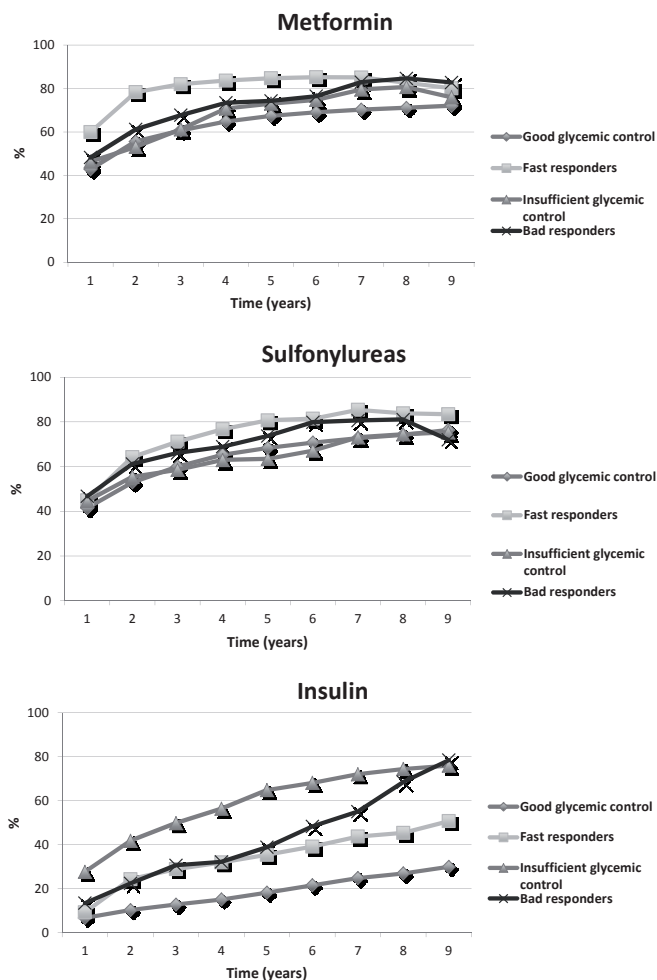


Figure 4. Proportion of metformin, SU or insulin usage according to different classes of HbA1c.

Sensitivity analyses Sensitivity analyses showed that in the cohort including only those patients who entered the DCS before 2006, the fast responders class disappeared and two classes showed sustained or deteriorating hyperglycemia over time (Figure 5).

Sensitivity LCGM analyses of newly diagnosed people with T2DM showed HbA1c classes identical to the classes within the total study population (data not shown).

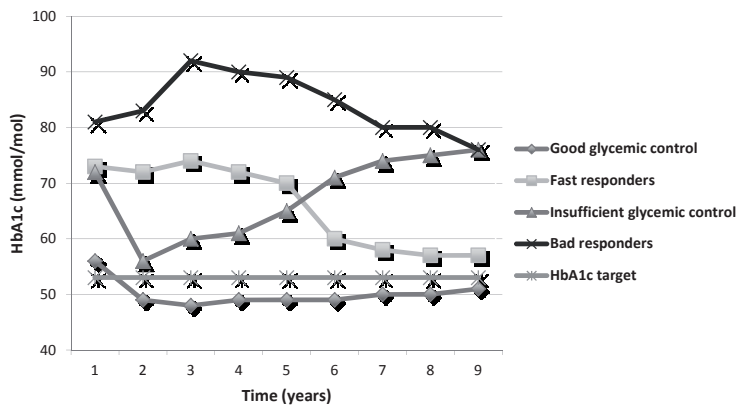


Figure 5. Classes with distinct trajectories of HbA1c in a subsample of patients who entered the cohort before 2006.

DISCUSSION

This study identified four classes of people with T2DM with distinct trajectories of glycemic control during a mean of 5.7 years of follow-up; a good glycemic control class, a fast responders class, an insufficient glycemic control class and a bad responders class. Higher HbA1c levels, a longer diabetes duration and younger age at baseline were associated with a more unfavourable course of glycemic control over time.

To our knowledge, this is the first study identifying classes with distinct trajectories of glycemic control in a clinical T2DM cohort. Existing studies have calculated a 'one size fits all' average HbA1c trajectory or have not used longitudinal measurements of HbA1c levels [13-17]. Considering the heterogeneous character of T2DM, the assumption that one homogenous trajectory represents the whole T2DM patient group may be too simplistic. Our classes represent glycemic control heterogeneity within primary diabetes care more accurately.

The good glycemic control class and the fast responders class represent the 'healthiest' and therefore most desirable classes from a clinical perspective. These classes represent the vast majority (91.3%) of the total cohort, indicating that most patients are likely to reach the recommended HbA1c target in the context of managed primary diabetes care. This proportion is higher than that resulting from a recent observational study from the United States (U.S.) [18], in which almost half of the U.S. people with T2DM did not meet the recommended HbA1c target. It is also higher as compared to Europe, where about 60% reaches HbA1c levels of < 58 mmol/mol (7.5%) [19-21]. The present study population consists of a well-treated group of people with T2DM, who were treated according to a managed care plan in the DCS. Starting at diabetes diagnosis, patients

receive an annual extended diabetes assessment at the DCS in addition to the diabetes care offered by the patients' GPs. Patients have a central role in their care and self-management is stimulated by providing education and information programs. Moreover, individual care plans are discussed with the patient and patients are encouraged to make their own choices with respect to treatment options and lifestyle behavior [22]. The organization of care within the DCS may be an important reason why the included patients are so well controlled. Therefore, these results might not be generalizable to other populations where glucose levels are controlled to a lesser extent. However, the clinical characteristics of patients who reached the recommended HbA1c target and characteristics of those who did not, are comparable to other observational studies [19-21]. Therefore, it is likely that the identified trajectories also exist in other T2DM populations, probably with dissimilar proportions across classes. Nonetheless, the existence of the identified classes needs to be confirmed in other clinical study populations.

Persons in the insufficient glycemic control class and the bad responders class included relatively more patients with a longer diabetes duration and who entered the DCS during the earlier years of the study. Sensitivity analyses showed that the fast responders class was not present in the group of patients who entered the DCS before 2006. Our findings confirm the results of previous studies [18,23] and may indicate that the proportion of patients with bad or insufficient glycemic control decreased during more recent years due to earlier referral and improved glucose management.

Our findings are in accordance with other studies [24-30] that reported an association between deteriorating glycemic control and an increased risk of microvascular complications. The fast responders class consisted mainly of newly diagnosed diabetes patients and had a higher baseline prevalence of microvascular complications compared to the good glycemic control class. Nevertheless, the prevalence of microvascular complications in the fast responders class immediately decreased following tight glycemic control. These findings confirm that strict glycemic control in newly diagnosed people with T2DM has a beneficial effect on a patient's risk of developing microvascular complications. This study did not investigate the pathways underlying hyperglycemia and the risk of developing microvascular complications. One suggested pathway is that hyperglycemia induces pathogenic mechanisms, such as systemic low-grade inflammation, oxidative stress and micro- or macrovascular endothelial dysfunction which itself are associated with micro- and macrovascular complications in individuals with T2DM [24,31,32].

A limitation of our study is that selective drop-outs may have occurred. However, since the proportion of dropouts did not differ across classes, it is unlikely that the occurrence of selective dropouts influenced the construction of classes within our cohort. Another limitation is that we did not have information on the development of macrovascular complications, neuropathy, lifestyle, treatment intensification and treatment adherence in the different classes. Year of onset

of diabetes was obtained by self-report, which might have led to less precise information on year of onset of T2DM. However, T2DM was only considered present when the criteria as described in the methods section were met, which were investigated by the GP. Therefore, and considering the relatively short diabetes duration at baseline, it is unlikely that the use of self-reported year of onset of T2DM influenced our findings. Another limitation is that HbA1c levels were only measured once a year. This might have led to less precise construction of the classes. However, as the HbA1c levels were quite stable throughout time, it is unlikely that missing intermediate information on HbA1c levels resulted in different trajectories.

Furthermore, the proportion of medication use might be an underestimation, since information about medication use was obtained via self-reporting. However, comparison of the diabetes medication with data from the PHARMO network showed an almost complete agreement. Therefore the degree of underestimation is probably negligible.

The use of LCGM as a method to define classes with distinct trajectories has some limitations. The first limitation concerns the complexity and flexibility of the model. There are numerous, somewhat arbitrary, choices to make and each decision could potentially influence the final number of classes. Furthermore, the extraction of the classes from the data does not prove the existence of multiple subgroups, but is a simplification of reality, which should be kept in mind when conducting LCGM. However, an advantage of LCGM is that categorization is not based on subgroups determined a-priori, but on trajectory characteristics of HbA1c derived from the data. Further, LCGM is focused on relationships among individuals, and makes it possible to categorize them in homogenous subgroups [8]. Strengths of this study include its large sample size with a short T2DM duration at baseline, standardized measurements of T2DM related risk factors and complications. The study was longitudinal in nature, with nine years of follow-up and multiple measurements of HbA1c from each participant, allowing identification of HbA1c trajectories.

To conclude, four classes with distinct trajectories of glycemic control were identified in a Dutch population of 5,423 people with T2DM. More than 90% reached the recommended HbA1c target and had a low prevalence of microvascular complications during an average of 5.7 years of follow-up. Patients within the insufficient glycemic control and the bad responders class had an increased prevalence of microvascular complications over time. These findings may be the first step towards personalized care and confirm that strict glycemic control, especially in newly diagnosed people with T2DM below the HbA1c target of ≤ 53 mmol/mol diminishes a patient's risk of developing microvascular complications. Patients with a longer duration of diabetes and a younger age before initiation of glucose management may require personalized care strategies to achieve tailor-made glycemic control and to decrease the risk of developing microvascular complications.

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Chapter 5

Real world evidence of suboptimal blood pressure control in patients with Type 2 Diabetes.

Iris Walraven, Ruth Mast, Trynke Hoekstra, AP Danielle Jansen, Simone P Rauh, Femke R Rutters, Amber AWA van der Heijden, Petra J Elders, Annette C Moll, Betina C Polak, Jacqueline M Dekker, Giel Nijpels.

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ABSTRACT

Background In order to eventually improve blood pressure (BP) management, the aim of this study was to identify subgroups of people with T2DM with distinct trajectories of systolic BP (SBP) levels. Subgroup characteristics were determined and the prevalence of complications and mortality rates over time in the different subgroups was investigated.

Research Design and Methods 5,711 people with T2DM with at least two SBP follow-up measurements were selected from a prospective T2DM cohort of 9,849 people with T2DM. The mean follow-up period was 5.7 years (range 2 - 9 years). Latent Class Growth Modeling was performed to identify subgroups of patients with distinct SBP trajectories. Subgroup characteristics were determined by multinomial logistic regression analyses.

Results Four subgroups with distinct SBP trajectories were identified. The largest subgroup (85.6%) showed adequate SBP control (at or around 140 mmHg) over time. The second subgroup (5.6%) were hypertensive in the first years, responded slowly to BP management and eventually reached SBP control. The third subgroup (3.4%) showed deteriorating hypertension during the first four years, then showed insufficient response to BP management. The fourth subgroup (5.4%) showed deteriorating hypertension over time. People with T2DM within subgroups 2-4 were significantly older, comprised more women, used more antihypertensive medication and had a higher prevalence of retinopathy, microalbuminuria and CVD mortality.

Conclusions More than 85% reached and maintained adequate SBP control. Subgroups with a more unfavourable course of SBP control also showed higher rates of microvascular complications and CVD mortality over time. This study identified important subgroups to target in order to improve BP management in people with T2DM.

INTRODUCTION

Hypertension is present in as many as 70% of the people with type 2 diabetes mellitus (T2DM) [1,2]. Untreated or poorly controlled hypertension in people with T2DM has an additive effect on long-term cardiovascular risk and accelerates the risk of developing micro- and macrovascular complications [1,3,4]. Furthermore, hypertension in people with T2DM is associated with an increased risk of mortality, with eight out of ten T2DM patients dying from cardiovascular events [5].

To decrease the risk of micro- and macrovascular complications, the current guidelines for blood pressure (BP) management in people with T2DM state that systolic blood pressure (SBP) levels should be lowered to at least 140 mmHg [6-9]. To further decrease the risk resulting from high BP levels, the initiation of antihypertensive therapy is indicated [6-10].

While lower SBP levels are proven to reduce the risk of complications [11]. The idea that “the lower the better” is beneficial for each T2DM patient, could be debated [12,13]. Some studies even suggest that too aggressive BP lowering in high-risk patients could do harm rather than to provide protection [12,14,15].

There are limited data from observational studies within clinical care available on the association between SBP levels, complications and CVD mortality in people with T2DM. Therefore, little is known about T2DM patient heterogeneity in the course of SBP levels. Identifying T2DM subgroups with a different course of SBP levels is important in order to eventually improve BP management and may provide more accurate insights into the relationship between SBP levels and outcomes. Latent class growth modelling (LCGM) is an innovative statistical method allowing subgroup (class) determination of people with T2DM with a distinct course of BP control over time [16].

The Diabetes Care System (DCS) West-Friesland in The Netherlands consists of a large primary care cohort of people with T2DM with a long-term follow-up and offers the unique opportunity to identify classes of people with T2DM with distinct SBP trajectories, which is the primary aim of this study. Subsequently, clinical characteristics and associations of class membership with outcomes were assessed.

RESEARCH DESIGN AND METHODS

An observational cohort study was performed with data from the DCS West-Friesland, described in detail elsewhere [17,18]. Briefly, the DCS organizes managed diabetes care in the region of West-Friesland in The Netherlands, a region with about 200,000 inhabitants, representative for a Caucasian population.

The DCS uses a managed care plan for people with T2DM with contracted health care providers in the region and is responsible for the quality of diabetes care. The diabetes care in the region encompasses the care provided by patients' general practitioners (GPs), according to the Dutch GP treatment guidelines for T2DM, and annual visits as organized centrally by the DCS for annual review assessments and patient education by the diabetes nurse and dietician. Results of the annual DCS visits and protocol driven therapeutic advices are provided to the patient's GP. The DCS maintains anonymous computer records and patients are informed on the use of these records for research purposes [17].

Study cohort

Figure 1 presents a flowchart of the study population. In the period between 1998 and 2011, 9,849 people with T2DM with different diabetes duration entered the DCS in different years. For each patient, the year of entry to the DCS was considered the baseline measurement (T1). Due to the open and dynamic nature of the cohort, the number of patients in the cohort decreased every follow-up year due to loss to follow-up, referral or death. In addition, 'newer' patients who entered the cohort at a later point in time had a shorter follow-up duration [17].

In order to accurately identify SBP classes, patients with a minimum follow-up of three years were included. Another precondition of performing LCGM is that information of at least 30% of the included study population is present during each follow-up measurement. The follow-up measurements from year 10 to 13 included less than 30% of the study population; therefore we

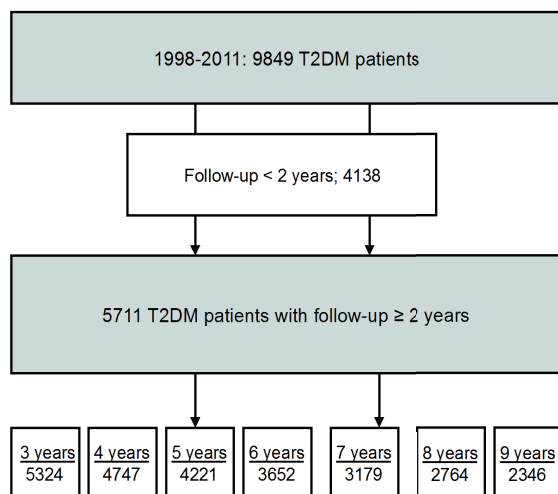


Figure 1. Flowchart of included patients within the study cohort

included the follow-up measurements until nine years of follow-up. The resulting study population ($n=5,711$) had a follow-up period ranging from three to nine years.

Measurements

Systolic and diastolic blood pressure levels were measured yearly, thrice, in a sitting position after 5 minutes of rest, using a random-zero sphygmomanometer (Hawksley-Gelman, Lancing, Sussex, U.K.). From 2003 on, an oscillometric device was used (Colin Press-Mate BP-8800, Komaki City, Japan; from 2009 on, Welch Allyn ProBP 3400, Skaneateles Falls, NY, USA). Mean blood pressure was calculated as the mean of three measurements. The absolute change in SBP between the baseline and the first year of follow-up was calculated. Pulse pressure was determined as SBP – DBP.

HbA1c level was assessed yearly with a DCCT standardized reversed-phase cation exchange chromatography (HA 8160 analyzer, Menarini, Florence, Italy). The HbA1c level was detected by a dual-wavelength colorimetric (415–500). The intra-assay coefficient of variation (CV) was 0.6% at a mean level of 4.9% and the inter-assay CV was 0.8 % at a mean level of 5.5% [17].

Weight and height were measured yearly (while patients were barefoot and wearing light clothing). *BMI* was calculated by weight in kilograms divided by the height in meters squared. *Total cholesterol level* was measured yearly using enzymatic techniques (Boehringer Mannheim, Mannheim, Germany).

Current medication use Use of cardiovascular and diabetes medication were obtained yearly by self-report.

Urinary albumin-creatinin ratio (UACR) in mg/mmol was determined yearly in an overnight, first-voided urine sample. Urinary albumin was measured by rate nephelometry (Array Protein System; Beckman Coulter, Fullerton, CA) with an assay threshold of 2 mg/L. Urinary creatinin was measured using a modified Jaffé test. *Microalbuminuria* was considered present if UACR > 2.0 mg/mmol [17]. *Retinopathy* From 1998 until 2000, fundus photography of both eyes was performed yearly with a Kowa Pro Fundus camera with a green filter (Kowa Optical Industry, Torrance, CA). From the beginning of 2000 until 2004, fundus photography of both eyes was performed with a nonmydriatic Canon CR5 camera (Canon Inc., Tokyo, Japan). From 2004, fundus photography of both eyes was performed using a nonmydriatic Topcon TRC NW 100 camera (Topcon, Tokyo, Japan). One photograph was centred on the macula and the other nasally with one optic disc diameter from the temporal side. All photographs were graded by an experienced ophthalmologist according to the EURODIAB classification score [19].

Mortality Information on CVD mortality until the first of January 2013 was derived from the municipal administration registries. Information on the cause of death was retrieved from medical records of general practitioners and from the local hospital. All causes of death were coded according to the International Classification of Diseases, Injuries and Causes of Death, ninth revision (ICD-9). Cardiovascular mortality and sudden death were regarded as CVD mortality and were defined as ICD-codes 390-459, 798, 427.4 and 427.5.

Drop-outs were identified as those who were lost to follow-up, e.g. due to referral to secondary care or migration.

Statistical analysis

Baseline characteristics were assessed and differences between the classes (mean (\pm SD), proportion or median in the case of a skewed distribution) were tested using ANOVA (continuous variables) and Chi-square tests (categorical variables). Overall p-values for between group differences are reported.

Latent Class Growth Modeling (LCGM) was used to identify classes of people with T2DM with distinct SBP trajectories. LCGM is a type of cluster analysis used to group patients into an optimal number of classes, each with a unique trajectory of SBP over time, by modeling heterogeneity in the time course. Each class has its own growth parameters (i.e. intercept, slope) and can be characterized by a distinct trajectory shape. To determine the optimal number of classes, a stepwise forward approach was taken starting with a model with one developmental pattern. Then, one class at a time was added. The optimal model is a model where patients within a class are most similar to each other and most different to patients in other classes. The model fit was assessed by the Bayesian Information Criterion (BIC) (where a lower BIC with a difference of at least 10 points indicates a better fit) and with posterior probabilities (where probabilities > 0.8 are recommended and a probability closer to 1 indicates a better classification) [16,17]. Also, the usefulness and clinical interpretation of each newly derived class were taken into account. The usefulness was assessed by considering the number of patients in each class (hereby rejecting small classes consisting of less than 1% of the total study population). The final number of classes was based on a low BIC score, good probabilities (> 0.8), usefulness, and clinically relevant differences between classes [17].

Class characteristics were investigated with multinomial logistic regression analyses, using a backward elimination method. In this analysis, we assessed which available patient and disease determinants at baseline were associated with membership in classes different than the reference class. The SBP class that had the most optimal SBP control was used as reference class. Associations of determinants with p-values < 0.10 were included in the final model.

Associations of class membership with the prevalence of retinopathy and microalbuminuria over time were studied using a binomial mixed modeling approach, accounting for both individual and time levels. Two models were constructed; the first model was adjusted for age, sex and time. The second model additionally accounted for confounding variables. Exponential beta's are reported and can be interpreted as odds ratios (OR) over time.

Cox survival analysis was performed to assess the risk of all-cause and CVD mortality in relation to class membership. All analyses were adjusted for age and sex, with subsequent analyses accounting for confounding variables.

Associations of class membership with cardiovascular medication use were studied constructing plots and graphically comparing differences between classes.

Sensitivity analyses were performed to investigate sex differences in SBP trajectories, by conducting LCGM and multinomial logistic regression analyses stratified for sex.

LCGM analyses were conducted with Mplus 5.21, binomial mixed modeling was performed with MLwin 2.25 and further analyses were performed with SPSS 20.0.

RESULTS

Baseline characteristics Table 1 presents baseline characteristics of the included study population. A total of 5,711 people with T2DM were included in the study (mean age of 60.6 years, 51% male, mean SBP 143 mmHg) with a mean follow-up duration of 5.7 years.

LCGM Figure 2 shows SBP trajectories of the identified classes. A four-class solution was found to be the best model according to the criteria described in the statistical analysis section. The largest class (85.6% of the people with T2DM) showed a stable trajectory of SBP control at or around 140

Table 1. Baseline characteristics of the different classes of systolic blood pressure trajectories.

| | Cohort | Adequate SBP control class | Delayed responders class | Insufficient SBP control class | Non-responders class | Overall P-value |
|-------------------------|---------------|----------------------------|--------------------------|--------------------------------|----------------------|-----------------|
| N (%) | 5711 | 4887 (85.6) | 319 (5.6) | 195 (3.4) | 310 (5.4) | - |
| Mean (SD) | | | | | | |
| Age (yr) | 60.6 (11.6) | 59.6 (11.5) | 66.4 (10.4) | 67.2 (10.8) | 65.9 (9.4) | <0.001 |
| Follow-up duration (yr) | 5.7 (2.3) | 5.6 (2.3) | 5.5 (2.3) | 6.3 (2.1) | 7.4 (1.1) | <0.001 |
| Diabetes duration (yr) | 1.0(0.2- 3.6) | 0.9 (0.17-3.3) | 1.2 (0.2 - 4.9) | 1.1 (0.2 - 5.2) | 2.0 (0.5 - 5.4) | <0.001 |

Table 1. Baseline characteristics of the different classes of systolic blood pressure trajectories. (continued)

| | Cohort | Adequate SBP control class | Delayed responders class | Insufficient SBP control class | Non-responders class | Overall P-value |
|---|--------------|----------------------------|--------------------------|--------------------------------|----------------------|-----------------|
| HbA1c (mmol/mol) | 57.8 (19.7) | 57.6 (19.9) | 57.4 (17.4) | 58.6 (19.1) | 60.0 (19.3) | 0.207 |
| Entry yr | 2003 (3.5) | 2004 (3.5) | 2004 (3.2) | 2003 (2.8) | 2000 (2.1) | <0.001 |
| BMI (kg/m ²) | 30.0 (5.4) | 29.9 (5.3) | 31.3 (6.0) | 30.8 (6.7) | 30.2 (5.3) | <0.001 |
| SBP (mmHg) | 142.7 (20.9) | 139.5 (17.8) | 182.1 (18.2) | 152.1 (23.8) | 148.7 (22.2) | <0.001 |
| Δ SBP (mmHg) | -1.9 (15.5) | -1.5 (14.5) | -15.1 (19.3) | 17.8 (18.6) | -2.4 (21.3) | <0.001 |
| DBP (mmHg) | 81.4 (10.9) | 80.5 (10.4) | 92.2 (12.2) | 83.2 (11.1) | 83.4 (11.8) | <0.001 |
| Total cholesterol (mmol/L) | 5.3 (1.2) | 5.2 (1.2) | 5.4 (1.2) | 5.3 (1.1) | 5.6 (1.1) | <0.001 |
| N (%) | | | | | | |
| Sex (% male) | 2899 (50.8) | 2589 (53.0) | 144 (45.1) | 63 (32.3) | 103 (33.2) | <0.001 |
| Current smoking (% yes) | 858 (15.0) | 741 (15.2) | 39 (12.2) | 32 (16.4) | 46 (14.8) | 0.002 |
| SBP ≤ 140mmHg (%) | 2816 (49.3) | 2635 (53.9) | 0 (0.0) | 60 (30.8) | 121 (39.0) | <0.001 |
| Prevalence of complications at baseline | | | | | | |
| Microalbuminuria (%) | 1102 (19.3) | 852 (17.4) | 106 (33.2) | 65 (33.3) | 79 (25.5) | <0.001 |
| Retinopathy (%) | 429 (7.5) | 339 (6.9) | 28 (8.8) | 23 (11.8) | 39 (12.6) | 0.007 |
| Use of (any) antihypertensive and diabetes medication at baseline | | | | | | |
| Antihypertensive use (%) | 2757 (48.3) | 2250 (46.0) | 195 (61.1) | 129 (66.2) | 183 (59.0) | <0.001 |
| Metformin use (%) | 2548 (44.6) | 2198 (45.0) | 140 (43.9) | 99 (50.8) | 111 (35.8) | <0.001 |
| SU use (%) | 2407 (42.1) | 2052 (42.0) | 126 (39.5) | 79 (40.5) | 150 (48.4) | 0.001 |
| Insulin use (%) | 473 (8.3) | 396 (8.1) | 26 (8.2) | 25 (12.8) | 26 (8.2) | 0.102 |

mmHg over time and was therefore named the adequate SBP control class. The second class (5.6% of the people with T2DM) started with hypertension (mean SBP 182 mmHg), responded slowly to BP management and reached SBP levels at or around 140 mmHg within seven years of follow-up and was therefore named the delayed responders class. The third class (3.4% of the people with T2DM) showed an inverse U-shaped course of SBP levels during nine years of follow-up, and was named the insufficient SBP control class. The fourth class (5.4% of the people with T2DM) showed worsening hypertension over time and was therefore named the non-responders class. Patients in the SBP control classes two to four, thus classes with inferior SBP control were older, were more often women, had a longer diabetes duration (except for the delayed responders class) and had higher BP levels at baseline (Table 1). Corresponding trajectories of DBP and pulse pressure levels were seen in all classes except for the non-responders class. Within the non-responders class, DBP levels remained stable while SBP and pulse pressure levels increased.

Class characteristics Table 2 shows the results of the multinomial logistic regression analysis. Patients within the delayed responders class had significantly higher baseline BMI levels and higher

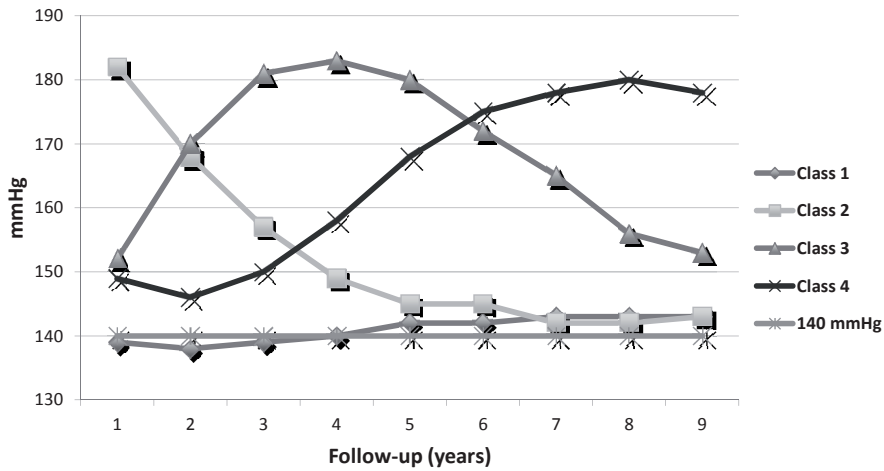


Figure 2. Classes of systolic blood pressure trajectories.

baseline SBP levels compared to the adequate SBP control class. Patients within the insufficient SBP control class had a statistically significantly higher likelihood of being women, of advanced age, of higher SBP levels and of higher BMI levels compared to patients within the adequate SBP control class. Patients within the non-responders class had a statistically significantly higher likeli-

Table 2. Multinomial logistic regression analyses associated with membership of different classes, compared to class 1 (adequate blood pressure control)

| Model 1 (OR (95% CI)) | |
|---|--------------------|
| Delayed responders class versus adequate control class | |
| Sex | 0.75 (0.53 - 1.05) |
| Systolic blood pressure (mmHg) | 1.11 (1.10 - 1.13) |
| Body mass index (g/m ²) | 1.05 (1.02 - 1.08) |
| Insufficient SBP control class versus adequate control class | |
| Sex | 2.03 (1.43 - 2.90) |
| Age (yr) | 1.04 (1.01 - 1.08) |
| Systolic blood pressure (mmHg) | 1.02 (1.01 - 1.03) |
| Cholesterol (%) | 0.86 (0.74 - 1.00) |
| Body mass index (g/m ²) | 1.05 (1.03 - 1.07) |
| Non-responders class versus adequate control class | |
| Sex | 1.97 (1.52 - 2.55) |
| Age (yr) | 1.14 (1.05 - 1.23) |
| Diabetes duration (yr) | 1.03 (1.02 - 1.05) |
| Systolic blood pressure (mmHg) | 1.02 (1.01 - 1.03) |

Multivariate analyses, corrected for age and sex showing determinants with *p*-values <0.10

hood of being female, of advanced age, had higher SBP levels and had a longer diabetes duration compared to patients within the adequate SBP control class.

Microvascular complications At baseline, classes with SBP control other than the adequate SBP control class had a significantly higher prevalence of microalbuminuria, compared to the adequate SBP control class (Table 1). Table 3 presents associations of class membership with retinopathy and microalbuminuria over time. Adjusted for confounding, the insufficient SBP control (OR 1.68 CI 1.18 to 2.37) and the non-responders class (OR 1.62 CI 1.28 to 2.05) showed a significantly increased risk of retinopathy over time. Microalbuminuria was significantly more present in all other classes, compared to the adequate SBP control class (Table 3).

Table 3. Associations of class membership with retinopathy and microalbuminuria

| | Delayed responders class (OR (95% CI)) | Insufficient SBP control class (OR (95% CI)) | Non-responders class (OR (95% CI)) |
|--|---|---|---------------------------------------|
| Retinopathy | | | |
| Model 1, adjusted for age, sex and time | 1.16 (0.86 - 1.57) | 1.84 (1.32 - 2.57) | 1.63 (1.28 - 2.08) |
| Model 1 + BMI, diabetes duration and HbA1c | 1.26 (0.94 - 1.69) | 1.68 (1.18 - 2.37) | 1.62 (1.28 - 2.05) |
| Microalbuminuria | | | |
| Model 1, adjusted for age, sex and time | 1.31 (1.05 - 1.63) | 1.86 (1.46 - 2.35) | 2.04 (1.68 - 2.46) |
| Model 1 + BMI, diabetes duration and HbA1c | 1.59 (1.27 - 2.00) | 1.86 (1.46 - 2.37) | 1.79 (1.47 - 2.18) |

Abbreviations: OR: odds ratio. The reference group is the Adequate SBP control group

All-cause and cardiovascular mortality Table 4 presents a cox proportional hazards model for all-cause and cardiovascular mortality. The non-responders class had a significantly lower risk of all-cause mortality (HR 0.67 CI 0.48 to 0.95) compared to the adequate SBP control class. Adjustment for potential confounders did not alter the results (HR 0.69 CI 0.48 to 0.98). Membership of the insufficient SBP control class was significantly associated with an almost twofold risk of cardiovascular mortality (HR 1.80 CI 1.10 to 2.96). The delayed responders class and the non-responders class had a similar cardiovascular mortality risk as compared to the adequate SBP control class. Accounting for confounding variables did not alter the results (Table 4).

Table 4. Cardiovascular mortality risk according to different subgroups compared to the Adequate SBP control group.

| | Delayed responders class (OR (95% CI)) | Insufficient SBP control class (OR (95% CI)) | Non-responders class (OR (95% CI)) |
|--|---|---|---------------------------------------|
| Adequate SBP control | | | |
| Model 1, adjusted for age and sex | 0.94 (0.67 – 1.32) | 1.30 (0.87 – 1.95) | 0.67 (0.48 – 0.95) |
| Model 1 + diabetes duration, BMI and HbA1c | 0.96 (0.65 – 1.43) | 1.39 (0.93 – 2.09) | 0.69 (0.48 – 0.98) |
| Cardiovascular mortality | | | |
| Model 1, adjusted for age and sex | 1.02 (0.64 – 1.76) | 1.72 (1.05 – 2.81) | 0.78 (0.50 – 1.22) |
| Model 1 + diabetes duration, BMI and HbA1c | 0.98 (0.57 – 1.67) | 1.80 (1.10 – 2.96) | 0.78 (0.49 – 1.24) |

Abbreviations: OR: odds ratio. The reference group is the Adequate SBP control group

Within the insufficient SBP control class, the course of SBP levels over time did not differ between those who died from cardiovascular events and those who did not (Figure 3).

Cardiovascular mortality rates increased steadily over time, with a slightly steeper increase in mortality from the sixth year of follow-up (data not shown).

Medication use In all classes, use of any cardiovascular medication increased over time. Classes with inferior BP control had the highest utilization of (any) antihypertensive drug. Use of two and

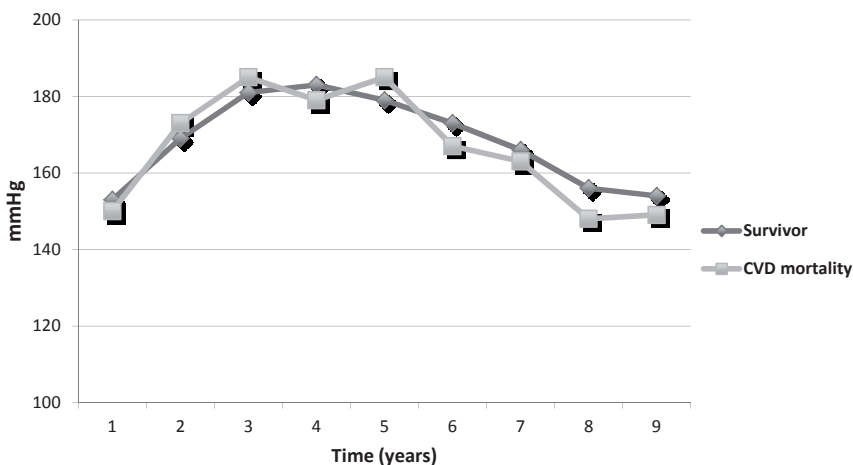


Figure 3. Systolic blood pressure levels of the insufficient SBP control class, stratified for cardiovascular mortality.

three or more antihypertensive drugs was most common within the delayed responders class and the insufficient SBP control class with $\pm 30\%$ of the patients using three or more antihypertensive drugs at nine years (data not shown).

Sensitivity analyses LCGM analyses stratified for sex showed no differences in SBP trajectories among men and women and did not materially change the results of the analyses (data not shown).

DISCUSSION

In the current study, we identified four T2DM classes with distinct trajectories of SBP control during a mean follow-up period of 5.7 years; an adequate SBP control class, a delayed responders class, an insufficient SBP control class and a non-responders class. People with T2DM within SBP control classes other than the adequate SBP control class were older, comprised more women, had higher BMI and SBP levels and had a higher prevalence of microvascular complications over time. The insufficient SBP control class showed an almost twofold increased risk of cardiovascular related mortality over time.

To our knowledge, we are the first to show T2DM patient heterogeneity in the course of SBP levels and to provide long-term proof of the real world effectiveness of the current BP guidelines in T2DM patients. Although more than 85% reached stable levels of SBP control at or around 140 mmHg, we also showed that there are certain groups that have insufficiently controlled SBP levels over time and for whom the current guidelines might not provide the best treatment strategy. The current guidelines are merely based on outcomes of randomized clinical trials (RCTs) [6,9,20]. Patients included in RCTs generally do not reflect the clinical T2DM population and represent only a highly selected patient group defined with detailed in- and exclusion criteria. Our results complement the results of several cross-sectional studies within clinical practice showing suboptimal BP control [21-24] and urge the need to consider real world clinical studies when providing BP management recommendations for clinical practice.

In our study, classes with suboptimal SBP control were significantly older (mean age 66 years), more likely to be female and had higher BP levels at baseline. Particularly older people with T2DM are mainly not included in RCTs. Older people with T2DM with uncontrolled hypertension represent an important subgroup to target in order to improve SBP control within primary care.

The delayed responders class and the insufficient SBP control class steadily used more antihypertensive drugs as compared to the adequate SBP control class. Although the use of antihypertensive drugs has a beneficial effect on BP control, it is often difficult to control BP levels using a

single drug. Therefore, combination therapy is advocated in people with T2DM with uncontrolled SBP levels [6,8-10,20]. Classes with inferior control indeed used combination therapy more often, indicating that clinical efforts were made to improve BP control. However, at nine years a maximum of 30% of the patients with inferior SBP control used three or more antihypertensive drugs. Because of the observational nature of the study, we cannot identify underlying reasons for the potential reluctance to initiate a third antihypertensive drug. More research is needed to identify reasons for not initiating a third antihypertensive drug.

The insufficient SBP control class showed an almost twofold increased risk of cardiovascular related mortality. This subgroup typically showed an inverse U-shaped course of SBP levels and mortality rates increased more steeply after SBP levels started to decline. Within this class, the course of SBP levels over time did not differ between those who died from cardiovascular events and those who did not; thereby reducing the likelihood that selective dropouts influenced the observed association. There is some validating evidence for our findings. Analysis of a T2DM cohort showed that the risk of death in elderly patients with T2DM increased by 15% for every 10 mmHg decrease in systolic BP [25]. Another study investigated blood pressure trajectories before death and showed that mean SBP levels declined in the years before death in patients with T2DM. This annual rate of decline was significantly higher than in the patients who remained alive [26].

Surprisingly, the non-responders class exhibited a higher risk profile and had a lower all-cause and cardiovascular mortality risk compared to the adequate SBP control class. The lower cardiovascular mortality risk in the non-responders class is contra-intuitive and could have been influenced by competing mortality risks. To exclude bias by selective loss to follow-up, the number of dropouts was compared in all subgroups and no statistically significant differences were seen. Based on these outcomes, we cannot exclude the risk that competing mortality risks biased our results. Furthermore, this finding remains contra-intuitive and more research needs to be performed to unravel underlying causes for this lower mortality risk.

Enrolment of patients was carried out between 1998 and 2011, a period in which SBP targets were more rigorous than nowadays (<130mmHg). This might have caused an overestimation of the finding that a very high proportion of the patients achieved adequate SBP control during follow-up. These proportions might not reflect current BP control in people with T2DM. Nonetheless, characteristics of people with T2DM with inferior SBP control are probably comparable.

The adequate SBP control class showed stable SBP control at or around 140 mmHg and showed a beneficial effect in terms of microvascular complications and cardiovascular mortality risk. These results are in line with large RCTs. The UKPDS study found that lowering SBP levels to a mean of 144 mmHg markedly reduced the incidence of micro- and macrovascular complications compared

to the group that achieved mean SBP levels of 154 mmHg during follow-up [1]. A retrospective subgroup analysis of the HOT trial showed a large reduction in CVD complications in people with T2DM with a mean achieved BP of 140/81 mmHg [27].

The non-responders class showed deteriorating SBP levels over time, while DBP levels remained stable. Consequently the pulse pressure within this class increased over time as well. This might indicate that arterial stiffness is the reason for uncontrolled BP levels within this group.

A limitation of our study is that we had neither information on treatment intensification nor on treatment adherence. Furthermore, the associations of class membership with the proportion of medication use might have been underestimated, since this information was obtained by self-report. Additionally, because of the observational nature of this study, our findings do not imply causality and we cannot explain the mechanisms underlying the observed associations.

Finally, the extraction of the classes from the data by using LCGM is no proof for the true existence of multiple subgroups. However, an advantage of LCGM is that categorisation is not based on subgroups determined a-priori on theoretical knowledge, but they are based on comparable trajectory characteristics within the data. Moreover, LCGM takes sensoring into account, thereby eliminating the chance that selective dropouts influenced the construction of classes [16].

Strengths of this study include its observational prospective design, its large sample size with standardized measurements of T2DM related risk factors and complications. Further, the availability of multiple measurements of SBP from each participant allowed identification of SBP control trajectories.

To conclude, we showed that, under the current guidelines, long-term SBP control is still suboptimal in people with T2DM treated within primary care. Even though more than 85% of the people with T2DM reached and maintained stable SBP levels at or around 140 mmHg during an average of 5.7 years of follow-up, classes with a more unfavorable course of SBP control showed higher rates of complications. The insufficient SBP control class showed an increased risk of cardiovascular related mortality over time.

We emphasize that more research needs to be performed to unravel underlying causes for the existence of classes with suboptimal SBP control within clinical practice in order to eventually improve SBP control and thereby decrease the risk of complications.

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Chapter 6

The use of antidepressants, anxiolytics and hypnotics in people with Type 2 Diabetes and characteristics associated with use: the Hoorn Diabetes Care System Cohort.

Ruth Mast, Simone P Rauh, Lenka Groeneveld, Anitra D Koopman, Joline W.J. Beulens, Aaltje P.D. Jansen, Marijke Bremmer, Amber van der Heijden, Petra J. Elders, Jacqueline M Dekker, Giel Nijpels, Jacqueline Hugtenburg, Femke Rutters.

Submitted.

ABSTRACT

Objective With depression being present in approximately 20% of people with type 2 diabetes mellitus (T2DM), we expect equally frequent prescription of antidepressants, anxiolytics and hypnotics. Nevertheless, prescription data in people with T2DM is missing and the effect of depression on glycemic control is contradictory. The aim of this study was to assess the use of antidepressants, anxiolytics and/or hypnotics in a population-based cohort of people with T2DM and to determine the socio-demographic characteristics, co-morbidities, T2DM medication and metabolic control associated with its use.

Research Design and Methods The use of antidepressants, anxiolytics and/or hypnotics in the year 2007-2012 was assessed in the population-based Hoorn Diabetes Care System Cohort from the Netherlands. The following characteristics were compared between users and non-users in the year 2011: age, gender, education, ethnicity, co-morbidities, T2DM medication, HbA1c and BMI.

Results From the 7,016 people with T2DM, 500 people (7.1%) used antidepressants only, 456 people (6.5%) used anxiolytics and/or hypnotics only and 254 people (3.6%) used a combination. Users were more often female, non-Caucasian and lower educated compared to non-users. Users of anxiolytics and/or hypnotics were older, had higher BMI, and more co-morbidities compared to non-users. Moreover, antidepressant users more often used insulin (27.2% vs. 21.5%). Finally, glycaemic control did not differ between users and non-users (51-52 mmol/mol vs. 52 mmol/mol).

Conclusions Compared to the prevalence of depression, use of antidepressants, anxiolytics and/or hypnotics was slightly higher in people with T2DM and while no differences in co-morbidities and HbA1c were observed between users and non-users, users were more frequently treated with insulin.

INTRODUCTION

In our current society, depression is present in approximately 20% of the people with type 2 diabetes mellitus (T2DM), twice as many when compared to the non-diabetic population [1]. Two recent meta-analyses have shown that depression increases the risk of developing T2DM and vice versa [2-4]. Similar reciprocal associations have been observed for anxiety, sleep disorders and T2DM [5-8].

Depression, anxiety and/or sleep problems are diagnosed using the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) [9,10], and are treated with psychotherapy, or pharmacotherapy when the patient is unresponsive to the latter [11]. First choice treatment is psychotherapy, while pharmacotherapy may possibly lead to poorer glycaemic control. However, studies on the effect of depression/ pharmacotherapy on glycemic control have been contradictory [12-15]. Despite the cautious treatment regimes, in Western society, antidepressants, anxiolytics and hypnotics are by far the most often prescribed drugs [14-16]: in the general population 6% is prescribed antidepressants and 7.5-9.9% are prescribed anxiolytics and/ or hypnotics [12,17].

While the prevalence rate of depression, anxiety and/or sleep disorders in people with T2DM is high (20%) [18,19], we expect equally frequent prescription of antidepressants, anxiolytics and hypnotics. One study from Finland reported that antidepressant use among men and women who develop T2DM was 2 times higher than that in non-diabetic individuals [20]. Nevertheless, to our knowledge prescription data of antidepressants, anxiolytics and hypnotics in people with T2DM are scarce. This may be due to the fact that people with T2DM are often excluded from trials on depression treatment [21]. In addition, all previous studies (5-8, 11-13) on the coincidence with T2DM, assessed depression, anxiety and/or sleep disorders by interview or questionnaire, with no information on pharmacological treatment. Our first aim is therefore to assess the use of antidepressants, anxiolytics and hypnotics in a population-based cohort of people with T2DM.

Characteristics of antidepressants, anxiolytics and/ or hypnotics use are well known in the general population [16,22,23]. Antidepressants, anxiolytics and/ or hypnotics are more often prescribed to women, compared to men [16,16]. Furthermore, lower education level, older age and non-Caucasian ethnicity have been associated with use of antidepressants, anxiolytics and/or hypnotics [16]. While people with T2DM often have a lower level of education and higher age, we expect higher levels of antidepressants, anxiolytics and/or hypnotics use in people with T2DM compared with the general population [22,23]. Up until now the characteristics of use of antidepressants, anxiolytics and/or hypnotics in people with T2DM has not been investigated.

However, identifying and treating depression, anxiety and sleep problems has become an increasingly important component of the diabetes management. Nevertheless, we do not know if

people with T2DM are more often treated with antidepressants, anxiolytics and/ or hypnotics and information on the determinants of use.

Therefore, the overall aim of this study was to assess the use of antidepressants, anxiolytics and hypnotics in a population-based cohort of people with T2DM and to determine the socio-demographic characteristics, co-morbidities, T2DM medication and metabolic control associated with its use.

RESEARCH DESIGN AND METHODS

Data source

Hoorn Diabetes Care System Cohort

Data were derived from the Hoorn Diabetes Care System (DCS) cohort, a prospective cohort using clinical care data, which is described in detail elsewhere [24]. In short, the DCS cohort uses a centrally organized managed care plan for treatment of people with T2DM with contracted health care providers. The organisation of the DCS is responsible for the quality of diabetes care in the region of West-Friesland in the Netherlands, a region with about 200,000 inhabitants. The DCS cohort encompasses the care provided by a patient's primary care physician, according to the Dutch treatment guidelines for T2DM [25]. The data from the annual assessment of the people with T2DM, which is organized centrally by the DCS, was used in this study.

Starting the 1st of October 1996, every year new people with T2DM enter the prospective dynamic cohort resulting in 9,118 people with T2DM with at least one measurement at the 31th of December 2012. For each patient, the year of entry to the DCS cohort was considered to be the baseline measurement. For our current study, we only excluded patients of whom we had no data on medication use (n=169, 50% male). Therefore, 8,949 patients were included in our current analyses. As the results of use of antidepressants, anxiolytics and/ or hypnotics over the years were very similar, we decided to present only the results of 2011. The year 2011 was the year with the most complete medication dataset as a result of the digital registration of the medication use implemented in this year. We used data from 2011 to study the characteristics between users and non-users resulting in 7,016 people with T2DM. The DCS cohort has anonymous computer records and people with T2DM were informed on the use of these records for research purposes. The study was approved by the Medical Ethical Committee of the VU University Medical Center.

Measurements

Medication Information on current medication use was registered yearly at the annual visit by checking the dispensing labels of the medication brought in by people with T2DM.

Antidepressants, anxiolytics and hypnotics We categorized antidepressants, anxiolytics and hypnotics based on their ATC-codes, namely N06A for antidepressants, N05B for anxiolytics and N05C for hypnotics and sedatives. Since the division between anxiolytics and hypnotics depends on the indication, which we did not have, we combined anxiolytics and hypnotics use into one group [26].

People using diazepam enemas and/ or hydroxyzine were not categorized as anxiolytic users, because diazepam enemas are more often prescribed for the emergency management of epileptic seizures and hydroxyzine is often prescribed against allergies. We lack information about indication and therefore we decided to combine the anxiolytics and hypnotics into one group

People with T2DM were divided into 4 groups: 1) no use of antidepressants, anxiolytics and/ or hypnotics; 2) only use of antidepressants; 3) only use of anxiolytics and/ or hypnotics; 4) combined use of antidepressants and anxiolytics and/ or hypnotics.

T2DM medication We defined three groups, based on ATC codes: diet only (no medication), insulin analogues (A10A) and oral glucose lowering agents (OGA, A10B). The OGA group contains the following OGAs: metformin, sulphonylurea, thiazolidinediones, alfa glucosidase inhibitors, DPP4 inhibitors, meglitinids and GLP-1 receptor agonists. Most patients using insulin analogues were using as well OGA.

Socio-demographic characteristics During the annual visit to the research centre, several socio-demographic factors were assessed in an interview, performed by the research nurse. Age and gender were self-reported. Education level was assessed using the question: 'What is your highest completed educational level?' The response alternatives were; 1:primary education, 2:secondary education – practical training, 3:pre-vocational secondary education 4: vocational training, 5: general secondary education or pre-university education, 6: professional university education and 7: university. Educational level was divided in 3 groups: low (level 1-2), middle (level 3-5) and high (level 6-7). Ethnicity was self-reported based on the questions: 'Indicate country of birth of your biological father and mother?'

Co-morbidities Information on history of cardiovascular disease, including myocardial infarction, transient ischaemic attack and stroke were self-reported.

HbA1c levels (%) were assessed from a fasted blood sample, using DCCT standardized reversed-phase cation exchange chromatography (HA 8160 analyzer, Menarini, Florence, Italy). *HbA1c* levels were detected using a dual-wavelength colorimetric (415-500). The intra-assay coefficient of variation was 0.6% at a mean level of 4.9% and the inter-assay CV was 0.8% at a mean level of 5.5%.

Weight and height Weight (kg) and height (cm) were measured annually during the visit in the research centre, while barefoot and wearing light clothing *Body Mass Index (BMI)* (kg/m^2) was calculated by weight in kilograms divided by the square of height in meters.

Statistical analysis

Characteristics of users and non-users were reported as mean and standard deviation for continuous variables and in the case of a skewed distribution, the medium with 25th and 75th percentile.

We compared characteristics of users and non-users, using descriptive summary statistics, including One-Way ANOVA for mean levels, with Chi-square tests (linear-by-linear association) for proportions and Kruskal-Wallis test for median levels.

Statistical analyses were performed with SPSS version 20.0 (SPSS Inc., Chicago, IL) and a two-sided p-value below 0.05 was considered statistically significant.

RESULTS

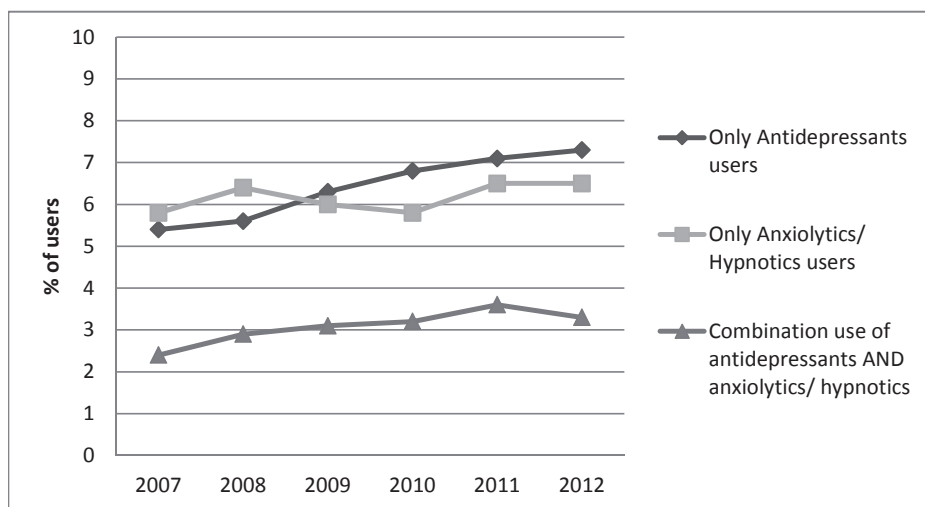
Population The characteristics of the population-based Hoorn Diabetes Care System Cohort of people with T2DM in the year 2011 are described in Table 1. The cohort consists of an equal amount of women and men with T2DM, with a mean age of 66.3 year (SD 11.7) and 22.5% of non-Caucasian ethnicity, while 40% had a low level of education. Most people with T2DM in the cohort used OGA's (60.1%) or insulin (combined with OGA (22.1%)) and the majority was overweight (30.2 kg/m^2 , SD 5.4), but well controlled as shown by a mean *HbA1c* level of 52 mmol/mol (6.9%).

Antidepressants and anxiolytics and/ or hypnotics use In our population-based cohort of people with T2DM, the average use of antidepressants, anxiolytics and/ or hypnotics was 17.2%: 7.1% used an antidepressant only, 6.5% used anxiolytic and/ or hypnotic only and 3.6% used a combination of antidepressants and anxiolytics and/ or hypnotics. Figure 1 showed the average use of antidepressants, anxiolytics and/ or hypnotics between 2007 and 2012. In the total population, the average use antidepressants was 5.4% in 2007 and increased to 7.3% in 2012. Also, the use of anxiolytics and/ or hypnotics increased, starting at 5.8% and increased to 6.5% in 2012.

Table 1 Patients characteristics and prevalence of antidepressants, anxiolytics and/or hypnotics use in the year 2011 from the Hoorn Diabetes Care System Cohort.

| | 2011 |
|--|------------------|
| Number of patients (n) | 7016 |
| Male (%) | 52.2 |
| Age (yr) | 66.3 ± 11.7 |
| HbA1c (mmol/mol (%)) | 52 (6.9) ± 1.1 |
| BMI (kg/m ²) | 30.2 ± 5.4 |
| Diabetes Duration (yr) | 6.0 (2.0 – 10.7) |
| Ethnicity (% Caucasian) | 77.5 |
| Education (%) | |
| Low | 46.3 |
| Middle | 39.1 |
| High | 14.6 |
| Only Antidepressants use (%) | 7.1 |
| Only Anxiolytics and/or hypnotics use (%) | 6.5 |
| Combination use (antidepressants and anxiolytics/ hypnotics) (%) | 3.6 |
| Co-morbidities (%) | 16.5 |
| Diet only (%) | 17.7 |
| Oral glucose lowering agents use only (%) | 60.1 |
| Insulin use (%) | 22.1 |

Abbreviation: Data as mean ± standard deviation or median (interquartile range). BMI: body mass index; HbA1c: glycated hemoglobin; SD: standard deviation.

**Figure 1.** Prevalent use of antidepressants, anxiolytics and/or hypnotics for the years 2007-2012 in the Hoorn Diabetes Care System Cohort.

With regard to patients using a combination of antidepressants and anxiolytics and/ or hypnotics, this increased from 2.4% in 2007 to 3.3% in 2012.

Socio-demographic characteristics of users Table 2 depicts the socio-demographic characteristics stratified for antidepressant, anxiolytics and/ or hypnotics users versus non-users in the year 2011. Compared to non-users, users were more often female: 44.3% of the non-users was female, while 61.8% - 74.8% of users was female ($p < 0.001$). We also observed differences in ethnicity with 21.2% of the non-users being non-Caucasian versus 26.2% - 29.8% of the users ($p < 0.001$) as well as education level, with 42.7% of non-users having a lower education level versus 48.0% - 52.8% of users ($p < 0.001$). Further, compared to non-users, those on anxiolytics and/ or hypnotics ($p < 0.001$) as well as combined users ($p < 0.02$) were significantly older. No significant age differences were observed in the users of antidepressants only .

Table 2 Patients characteristics stratified by antidepressant, anxiolytics and/or hypnotics use in the Hoorn Diabetes Care System Cohort in the year 2011 (n=7,016).

| | Non-users | Antidepressants users | Anxiolytics/ Hypnotics users | Combined use of antidepressants AND anxiolytics/ hypnotics |
|---|------------------|-----------------------|------------------------------|--|
| General Characteristics | | | | |
| Number of patients (n), (% of total number of patients) | 5806 (82.8) | 500 (7.1) | 456 (6.5) | 254 (3.6) |
| Male (%) | 55.7 | 38.2* | 38.2* | 25.2* |
| Age (yr) | 65.9 ± 11.5 | 64.7 ± 13.0 | 71.7 ± 11.4* | 68.1 ± 13.2* |
| HbA1c (mmol/mol (%)) | 52 (6.9) ± 1.1 | 52 (6.9) ± 1.1 | 51 (6.8) ± 0.9 | 52 (6.9) ± 1.0 |
| BMI (kg/m ²) | 30.1 ± 5.4 | 31.2 ± 5.7* | 29.9 ± 5.2 | 31.4 ± 5.4* |
| Diabetes duration (yr) | 5.9 (2.0 – 10.5) | 5.0 (1.8 – 10.2) | 7.0 (2.8 – 11.70)* | 6.0 (2.8 – 10.6) |
| Socio-Demographic Characteristics | | | | |
| Ethnicity (% Caucasian) | 78.8 | 73.8* | 70.2* | 70.9* |
| Education (%) | | | | |
| Low | 44.7 | 51.7* | 54.7* | 60.1* |
| Middle | 39.9 | 38.8* | 34.5* | 30.0* |
| High | 15.5 | 9.5* | 10.8* | 9.9* |
| Co-morbidities | | | | |
| Co-morbidities (%) | 15.4 | 17.2 | 26.8* | 20.1 |
| Diabetes Treatment | | | | |
| Diet only (%) | 18.2 | 16.6* | 14.9 | 14.2 |
| Oral glucose lowering agents use only (%) | 60.3 | 56.2* | 62.3 | 60.2 |
| Insulin use (%) | 21.5 | 27.2* | 22.8 | 25.6 |

Abbreviation: BMI: body mass index; HbA1c: glycated hemoglobin; SD: standard deviation.

*Significantly different from no antidepressant/ anxiolytics/hypnotics users. It is possible that patients are using insulin in combination with oral glucose lowering agents.

Co-morbidities Non-users had less co-morbidities (myocardial infarction, transient ischaemic attack and stroke), compared to people with T2DM on anxiolytics and/ or hypnotics (15.4% vs. 26.8%, $p < 0.001$). No differences in co-morbidities were observed in non-users versus antidepressant or combined users.

T2DM treatment and glycaemic control Finally, compared to non-users, those people using antidepressants more often used insulin as T2DM treatment (21.5% vs. 27.2% $p < 0.001$). No differences were observed in T2DM treatment between non-users and anxiolytics and/ or hypnotics users. Additionally, no significant differences were observed in continuous HbA1c or cut-off variables for HbA1c levels (≥ 53 mmol/mol) between users and non-users. With regard to BMI, compared to non-users, users of antidepressants had significant higher BMI levels compared to non-users (31.2 kg/m² vs. 30.1 kg/m², $p < 0.001$).

DISCUSSION

The aim of this study was to assess the use of antidepressants, anxiolytics and hypnotics in a population-based cohort of people with T2DM and to determine the socio-demographic characteristics, co-morbidities, T2DM medication and metabolic control associated with its use.

We observed that 17.2% of all people with T2DM used either antidepressants (7.1%), anxiolytics and/ or hypnotics (6.5%) or a combination of these medications (3.6%). In contrast to our expectations, antidepressants, anxiolytics and/ or hypnotics use was slightly higher in people with T2DM, compared to the general population in which 6% is prescribed antidepressants and 7.5-9.9% anxiolytics and hypnotics [12,17].

In concordance with studies in the general population, we observed that people with T2DM using antidepressants, anxiolytics and/ or hypnotics were more often female, older, non-Caucasian and had a lower level of education, compared to non-users [16,17,27]. Several possible reasons have been offered in literature, first women more often suffer from anxiety and depressive disorders, compared to men [28]. Second, women are more likely to use health services for mental problems and thus depression will more often be diagnosed and treated in women [29].

In contrast to earlier research in elderly people with T2DM, we did not observe more co-morbidities in users of antidepressants [30,31]. An explanation for this may be that our cohort was younger, relatively healthy and metabolically well-controlled. We did however observe that anxiolytics and/ or hypnotics users had more co-morbidities compared to non-users. This is in accordance with literature in the general population [32].

Furthermore, we were the first to observe with regard to T2DM medication, people with T2DM using antidepressants were more frequently treated with insulin, compared to non-insulin users. This is in accordance with other literature on the association between depression and T2DM [33,34] and may reflect disease progression. Insulin-treated people with T2DM often have a longer disease history, including poorer glycemic control and chance on co-morbidities [33-35,35].

Finally, with regard to metabolic status, no differences in HbA1c level were found between users and non-users. Earlier studies reported contradictory findings on the effects of antidepressants, anxiolytics and/ or hypnotics use on HbA1c levels [9,36,37]. Two longitudinal studies in people with T2DM and one meta-analysis from studies in the general population reported that depression was associated with poorer glycaemic control [9,36,37], while one study reporting a difference of 6 mmol/mol (0.5%) in HbA1c levels when comparing people with T2DM with and without depressive symptoms (17). However, another study observed no differences in glycaemic control (18). Our results support the earlier null-findings, the difference with studies that did find an association may be explained by cohort differences, we are one of the few to have an unselected, population-based cohort of people with T2DM.

This study has several limitations that need to be discussed. First of all, we lack information about indication and therefore we decided to combine the anxiolytics and hypnotics into one group [26]. Several anxiolytics, such as oxazepam, can be prescribed in case of anxiety, but also in case of sleep disorders. Further, antidepressants can be prescribed for other disorders than depression alone (for example neuropathic pain), but also in cases of anxiety. Also, people may be afflicted by the disease but not have been diagnosed. Therefore, our current study is not informative on disease prevalence and on the causal effect of medication or the disorder itself on T2DM. We therefore need longitudinal research in large cohorts of people with T2DM, to study the effect of antidepressants, anxiolytics and hypnotics use on glycaemic control.

The strengths of our study are that we were the first to investigate and report on the prevalence of antidepressants, anxiolytics and/ or hypnotics use, as well as differences in socio-demographic, co-morbidities, T2DM medication and metabolic status between users and non-users in a population-based cohort of people with T2DM. Thereby, this study has a large sample size ($n > 5000$), prospective study design, and comprehensive information on clinical variables. All information has been accurately registered and is therefore unique for a care-based cohort.

We conclude that compared to the prevalence of depression, use of antidepressants, anxiolytics and/ or hypnotics was slightly higher in people with T2DM and while no differences in co-morbidities and HbA1c levels were observed between users and non-users, users were more frequently treated with insulin.

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Chapter 7

Primary care physicians related barriers to
implementation of a web-based guided insulin
self-titration program in people with Type 2
Diabetes.

Ruth Mast, AP Danielle Jansen, Maaïke E Muntinga, Petra JM Elders, Jacqueline G
Hugtenburg, Giel Nijpels.

Submitted.

ABSTRACT

Background This study investigated the barriers to implementation among primary care physicians (PCPs) of a web-based insulin-titration self-management program (Di@log) for people with suboptimal controlled type 2 diabetes (T2DM). In a pilot study of Di@log, people with T2DM initiating insulin, adopted the program: they were satisfied with the user-friendliness and content.

Research Design and Methods Barriers to implementation of the web-based insulin-titration self-management program in primary care in the Netherlands were investigated by means of semi structured telephonic interviews with 12 PCPs who participated in the Di@log study, followed by a focus-group discussion with 7 PCPs.

Results PCPs stated that the main barriers to implementation of Di@log were related to the interoperability of the program with the PCPs own electronic patient information system. Moreover, PCPs assumed only a small number of people with T2DM are suitable for programs such as Di@log (as the majority of people are too old, lack computer skills, and are not eligible for insulin). PCPs thought that tailored care for this small number of people with T2DM would be time-consuming. In addition, PCPs/ Nurse practitioners wanted to control the insulin dose-adjustment themselves (16.7%). Forgetting the study was reported by 58.3% of the PCPs/Nurse practitioners.

Conclusions The most important lesson to be learned was to investigate the potential barriers that PCPs may face *before* implementing an e-health program in order to a) try to embed and tailor a program to the PCP organisation b) go/no go: decide on not to implement if doubts exist about embedding or need is lacking. Other option is to change the setting of implementation towards a setting facilitating embedding or towards a setting with an existing need for the e-health application.

INTRODUCTION

Diabetes Self-Management Education (DSME), including interactive behaviour change technology (IBCT), is one potential resource for improving diabetes management. In general it assists people with T2DM and their clinicians in monitoring changes in health and self-care needs, supports patients' efforts to make behaviour changes by promoting health and effective self-care, and enhances communication between people with T2DM and potential supports for their disease management [1-5].

The use of DSME in T2DM showed inconsistent results with respect to reducing HbA1c and other clinical outcomes such as weight loss and physical activity [1-6]. Self-titration of insulin therapy can be considered as DSME (i.e. self-monitoring of blood glucose and self-adjustment of insulin dose) and fits into the patient empowerment approach. This approach was derived from the idea that, caregivers are the experts on diabetes care, but patients are experts on their own life and should therefore be the primary decision-makers in control of their diabetes [7]. We designed the Di@log program which provides a facilitated way for self-monitoring and evaluation of glycemic control through feedback on input of glucose values by a web-based program.

This concept was strengthened by the results of a pilot study on people with T2DM' and PCPs' adoption of Di@log [8]. Participating people with T2DM initiating insulin were satisfied with the user- friendliness and content of the web-based program. Moreover, 64 primary care physicians (PCPs) were willing to participate in the RCT that evaluated the Di@log program.

Results Di@log RCT

36 PCPs participated in the Di@log study and included 13 people with T2DM during follow up (control group n=8, intervention group n=5). The HbA1c values at baseline were 92 mmol/mol for the intervention group and 68 mmol/mol for the control group. After three months of follow up the HbA1c levels decreased (68 mmol/mol in the intervention group, 65 mmol/mol in the control group (not published)

Despite the promising pilot, two years after the start of the RCT, an insufficient number (n=13) of people with T2DM was included in the RCT. We hypothesized that the successful implementation of Di@log was hampered by physician related factors. The barriers of PCPs to implement IBCT such as the Di@log program have not been investigated previously. Therefore, the present study investigated the PCP related barriers to implementation of Di@log.

RESEARCH DESIGN AND METHODS

To investigate the barriers to implementation of the web-based insulin-titration self-management program in the Netherlands, semi structured telephonic interviews were held with 12 primary care physicians (PCP) who participated in the Di@log study that evaluated the program. Later on, a focus-group discussion with PCPs not involved in Di@log was held in order to explore PCPs' potential barriers towards the web-based insulin-titration self-management program. The focus-group discussion was held with the use of a validated checklist, based on the theory of adoption and successful implementation of innovations [9]

The intervention: Di@log insulin-titration self-management program

Self-management of participants was supported by a website (www.diep.info) informing participants about insulin use, skills and knowledge needed for insulin injections: materials, techniques, injection places, storage of insulin, influence of physical activity and diet, self-monitoring, how to make a standardized day curve, hypo- and hyperglycaemia, influence of exercise and illness on insulin use.

In addition, participants were educated on how to use the insulin-titration self-management program. They learned how to fill in glucose values, what happens if they fill in a glucose value, how to respond on the feedback, how to monitor the glucose and adjust the insulin and where to find additional information on the website (provided by www.diep.info). The internet program was accessible through a log-in procedure, requiring a log-in name and a password.

The PN and PCP instructed the participants to start with 10 IE insulin glargine at bedtime, and subsequently measure fasting blood glucose (FBG) every morning through a finger prick and to import the glucose value of this finger prick in Di@log. Participants received tailored feedback based on the glucose level by means of a graph (day curve) and a dose advice. The dose advice entailed:

- + 4 IE when FBG exceeded 20 mmol/l (in addition, the patient consulted the PCP)
- + 4 IE when FBG exceeded 10 mmol/l for 2 consecutive days
- + 2 IE when FBG was in the range 7-10 mmol/l for 2 consecutive days
- - 2 IE when FBG was in the range 2.5-4 mmol/l for 2 consecutive days
- - 4 IE when FBG was below 2.5 mmol/l for 2 consecutive days.

A "digi-appointment" (an obligatory appointment with the internet program) was made when the participant was required to measure a new FBG and to adjust the dose of insulin or when a new day curve had to be made. If the insulin dose exceeded 80 IE, the participant was asked to make a 5 points day-curve and to contact the PCP, who decided on the insulin regimen needed. The

5-points day-curve will be checked by the program for deviant scores. Dependent of the value of one of the measured glucose values, the program automatically responded with a feedback question (whether the participant has an explanation or not when a measurement is too high or too low) and according to that response, gave advice on the concerning item (e.g. adjustment of diet or increase of physical activity) and also advised to repeat the day-curve within one week or to contact the PCP in case of no explanation.

For example, if the FBG was more than > 20 mmol/l the participant had to answer the following question: "This glucose value is very high. Do you have a reason for it?" Several suggestions were given (stress, illness, too less insulin injected).

When all measurements were within the range of 4 - 8 mmol/l, the advice was given that because of a stable insulin dose is reached, only once a week a FBG had to be measured from then on. The diary could still be used. It was advised to make a day-curve before the 3-monthly visits to the PCP or PN.

When the level of FBG was < 2.5 mmol/l or the participants showed symptoms of hypoglycaemia, the participant should take 5 dextrose tablets (or lemonade, or (non-diet) soft drink). After 15 minutes the participants had to repeat this test. If the FBG level was still too low the participant should take a sandwich and test again after 30 minutes etc. until the blood glucose had raised.

In case of problems, participants contacted their practice nurse (PN) or PCP (they had access to the data of their patients by a log-in procedure).

Because of safety reasons the following construction was incorporated in the program: When the participant does not comply with the digi-appointments: after 3 reminders a message is sent to the PCP. In cases when contact with the PCP was advised an alert was sent to the PCP. The initiative was with the participant, but the PCP had the ability to contact the participant.

Telephonic interview

25 PCPs and nurse practitioner (NPs) were asked to participate in a telephonic interview. A first round of semi structured interviews was held until saturation was reached. The interview protocol consisted of questions for reasons of implementation failure.

The barriers from the six semi structured interviews were listed and labelled (in three groups: perspective of PCPs on the participants, practice-dependent reasons and study-dependent reasons).

Subsequently, another six telephonic interviews were performed with other PCPs and NPs. Hereby we were able to confirm the reasons distilled from the first round of interviews, and to add other reasons for recruitment failure, followed by the question if they could think of additional reasons for the low recruitment of participants in the study. The interviews were held and analysed by JvdB. The data collected by the interviews were assessed using descriptive statistics: the frequencies of the reasons are shown as outcome.

Focus –group discussion

A focus-group discussion with PCPs was conducted, moderated by MRM. This method was chosen to allow participants to interact with each other about barriers to implementation of the web-based insulin-titration self-management program. Seven PCPs from Amstelveen were invited to participate in this focus-group discussion. Prior to the discussion, participants gave oral consent, and they were assured that all comments would remain confidential. First there was a short presentation about the web-based insulin-titration self-management program. Based on the checklist of successful health services innovations implementation of the Netherlands Organisation for Health Research and Development an interview guide (9) was used to get insight in the PCP perspectives on the program. This guide focused on the perceived benefits and burden requirements of the PCPs in the web-based insulin-titration self-management program. Examples of questions asked: Is it possible to combine the Di@log program with usual care, Is there a need for a program like Di@log, Do you think the Di@log program is easy, and not to complex?

The focus group discussion was audio recorded and afterwards transcribed. Two researchers (APDJ and MRM) coded the data independently to ensure the reliability and accuracy of the coding process, afterwards themes were identified and a consensus meeting was held.

RESULTS

In the following sections, we first describe the experiences of the PCPs and NPs who participated in the Di@log program. Subsequently, we describe the results of the focus-group discussion with PCPs who did not participate in the Di@log program.

Telephonic interviews Twelve interviews with PCPs and NPs to identify the reasons for not implementing the web-based insulin-titration self-management program in the practice were conducted. Table 1 shows an overview of the nature and frequency of reasons for not implementing the web-based insulin-titration self-management program. The reasons most frequently quoted were:

Table 1 Reasons reported by PCPs in telephonic interviews for not including patients in the Di@log Study.

| PCP perspective of the participants | N (%) | Intervention | Control |
|---|--------------|---------------------|----------------|
| Participants are not eligible for insulin therapy | 10 (83.3) | 6 | 4 |
| Participants do not have computer or internet skills | 10 (83.3) | 4 | 6 |
| Participants do not want to participate in this study | 3 (25.0) | 2 | 1 |
| Participants do not speak Dutch | 2 (16.7) | 0 | 2 |
| Participants fear insulin therapy | 2 (16.7) | 0 | 2 |
| Participants' compliance to treatment is insufficient | 1 (8.3) | 0 | 1 |
| Practice-dependent | N (%) | Intervention | Control |
| PCP/ NP forgets study | 7 (58.3) | 4 | 3 |
| Insulin glargine is not the preferred insulin | 2 (16.7) | 1 | 1 |
| PCP/ NP want to control the insulin dose-adjustment | 2 (16.7) | 1 | 1 |
| Another study is performed in the practice | 1 (8.3) | 1 | 0 |
| PCP/ NP feels not familiar with the study | 1 (8.3) | 1 | 0 |
| Insulin therapy is delayed by another discipline (e.g. internal medicine) | 1 (8.3) | 1 | 0 |
| Study-dependent | N (%) | Intervention | Control |
| Study is a generation too early | 6 (50.0) | 3 | 3 |
| Many inclusion criteria | 3 (25.0) | 1 | 2 |

'People with T2DM are not eligible for insulin therapy' and 'People with T2DM lack the required computer skills.'

In addition, PCP/ NP wanted to control the insulin dose-adjustment them-selves. Forgetting the study was reported by 58.3% of the PCPs/NPs. In six interviews PCPs reported that the program was too innovative and it was suggested that the program could possibly succeed in a next generation of people with T2DM, as they may have more of the required computer skills in the future.

Focus-group In total, the focus group discussion yielded 8 unique themes regarding the barriers to implementation of a web-based insulin-titration self-management program. The eight themes were subdivided in three barriers: 'the PCPs perspective of the participants', 'practice-dependent reasons for non-adherence' and 'study-dependent reasons for non-adherence'.

PCPs perspective of the participants

Small target population The small target population of people with T2DM that were suitable for a program like Di@log was mentioned as a potential problem: *'It's suitable for a small population.'* PCPs think the program is therefore time-consuming.

Computer skills The computer skills of people with T2DM were mentioned as a potential problem in the inclusion of participants in a web-based insulin-titration self-management program: *'A lot*

of older people are not used to work with a computer'. However, a part of the PCPs consider this not as the main problem: 'There is a group of older people with T2DM, what you do not expect, who can work very well with a computer'. The PCPs judged that most people with T2DM do not appreciate a program like this.

Practice- dependent reasons for non-adherence

Time-consuming When PCPs were asked how they would feel about using a web-based insulin-titration self-management program, almost all mentioned it is more time consuming for the PCP: 'Only extra difficult for our self, you have to go to a website.'

Interoperability In addition, according to the PCPs, the interoperability of the web-based program with their own electronic patient information system is a problem: 'The Di@log program does not match with the electronic patient information system, they should integrate these programs. In the end it is as much time-consuming as usual care.'

Study-dependent reasons for non-adherence

No need for a program PCPs who saw no added value of using a web-based insulin-titration self-management program typically were content with current diabetes management practice: 'No need for a program like Di@log. There is no problem. The usual care is oke.'

Table 2 Quotes of PCPs sorted by main barriers for not implementing Di@log.

| Barriers | Quote |
|---------------------------|--|
| Computer Skills | 'A lot of older people are not used to work with a computer.' 'If the web-based insulin-titration program is working well, it seems to me very easy.' 'There is a group of older people with T2DM, what you don't expect, who can work very well with a computer'. |
| Time-consuming for PCP | 'Only extra difficult for our self, you have to go to a website.' 'Only extra work for the PCP' . 'Again something extra.' 'Less people with T2DM are suitable for the program, so not much time is needed'. |
| No need for a program | 'No need for a program like Di@log. There is no problem. The usual care is oke'. |
| Small target population | 'It's suitable for a small population.' 'You have to arrange things by yourself. It is not suitable for everybody'. |
| Deviation from usual care | 'It is completely different than usual care'. |
| No financial profit | 'There is no financial profit, the NP still has to check these patients if everything is oke'. |
| Interoperability | 'Another password.' 'The Di@log study does not match with the electronic patient information system, they should integrate these programs. In the end it is as much time consuming as usual care'. |

Table 2 Quotes of PCPs sorted by main barriers for not implementing Di@log. (continued)

| Barriers | Quote |
|---------------------------------|--|
| Choice of Lantus not acceptable | <i>'It should not be linked at Lantus.'</i> <i>'This is completely unacceptable.'</i> <i>'I am not prescribing Lantus.'</i> <i>'You can't follow the PCP guidelines.'</i> |

Choice of Lantus® Some PCPs expressed their difficulties in the choice of the insulin Lantus® because Lantus® is not a first choice insulin: *'You can't follow the PCP guidelines.'* Other PCPs mentioned they never were prescribing Lantus®: *'I am not prescribing Lantus.'*

Nevertheless, the PCPs conclude that the program may contribute to the quality of care and satisfaction with care of the small group of people that is able to use the program (see Table 2).

DISCUSSION

The objective of this study was to investigate barriers in PCPs to implementation of a web-based insulin-titration self-management program. Although the program was adopted by people with T2DM and potentially successful in decreasing HbA1c values, PCPs did not adopt the web-based insulin-titration self-management program. The main barriers were related to the interoperability of the program with the PCPs own electronic patient information system. PCPs assumed only a small number of people with T2DM suitable for a program like this (people with T2DM are too old, lack computer skills, and are not eligible for insulin). PCPs considered tailored care for this small number of people with T2DM time-consuming.

Research showed that the implementation of DSME (e-health programmes) in primary care practices is complex and time-consuming [10-12]. In one of the studies, limited readiness for innovation among PCPs also appeared a barrier for implementation of an DSME program [13]. Another study confirmed the importance of a comprehensive anticipation of stakeholders' needs and preferences, as addressing only the needs of the participants group may not satisfy the needs of the PCPs [11].

The barriers of PCPs to implement DSME such as the Di@log program, have not been investigated previously. In the focus-group discussion the PCPs were of the opinion that there is no need for a program like Di@log. To overcome the barriers of PCPs to implement an e-health program in future, it is important to investigate these barriers, for example with a validated check for innovations [9].

Some limitations of the study need to be acknowledged. Not all participating PCPs were interviewed by telephone. Therefore it is possible that not all reasons for not implementing the web-based insulin-titration self-management program were collected. However, to overcome this limitation and to get insight into the opinion of PCPs on the implementation of the web-based insulin-titration self-management program, we performed a focus-group discussion. The telephonic interviews were not recorded on tape. Furthermore, it is possible that participating PCPs answered with socially desirable answers instead of their real opinion. Therefore it is possible that the results were less reliable.

In conclusion, the most important lesson to be learned was that preceding the implementation of DSME (e-health programs) and in order to tailor e-health programs, perceptions, opinions, beliefs and attitudes towards these programs must be investigated in all target groups (in Di@log: PCPs and people with T2DM). Other option is to change the setting of implementation towards a setting facilitating embedding or towards a setting with an existing need for the e-health application.

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Chapter 8

Amsterdam Tool for clinical medication review:
development and testing of a comprehensive
tool for pharmacists and general practitioners.



Ruth Mast, Abeer Ahmad, Sacha C Hoogenboom, Walter Cambach,
Petra JM Elders, Giel Nijpels, Jacqueline G Hugtenburg.

ABSTRACT

Background Drug-related problems are prevalent among older patients, and substantially increase the risk of morbidity, (re-)hospitalisation and mortality. To detect drug-related problems and optimize treatment primary caregivers should periodically review the medication of older patients. The aim was to develop a structured, comprehensive but practicable tool to facilitate and support the reviewing of medication of older patients with a chronic disease by pharmacists and general practitioners.

Research Design and Methods A tool facilitating clinical medication review by community pharmacists was developed on the basis of treatment guidelines, literature data on drug-related problems. For the identification of drug-related problems from the patient's perspective, a script for structured interviews was developed. The tool was optimized by means of a Delphi method with an expert panel and testing in a trial.

Results The medication review tool consists of a comprehensive checklist of 124 drug-related problems divided by 20 sections according to physiological systems and diseases, and includes a structured interview script for a patient interviews.

Conclusions A structured, comprehensive and practical tool to assist pharmacists and general practitioners to perform clinical medication review including a list of potential drug-related problems in older patients with chronic disease, as well as a script for structured patient interviews, was developed.

INTRODUCTION

Drug-related problems (DRPs) are events or circumstances related to drug therapy that actually or potentially interfere with desired health outcomes [1-3]. DRPs are prevalent among older patients and substantially increase the risk of morbidity, (re-) hospitalization and mortality [4,5]. DRPs include ineffectiveness of treatment, occurrence of adverse reactions and dissatisfaction of patients with their therapies [3]. DRPs may be the result of a wide variety of causes including medication errors, frequent medication changes, specific drug effects and drug combinations, inappropriate use of medicines, inappropriately prescribed medicines, and non-adherence to treatment [3,6]. Factors increasing the risk of DRPs are advanced age, comorbidity, polypharmacy and a lack of coordination between different caregivers after having initiated, altered or discontinued treatments [6].

Over the years, substantial effort has been made to prevent and detect potentially inappropriate medicines (PIM) [6,7]. Several sets of explicit criteria, of which the Beers criteria are the oldest and best known, have been developed to assist caregivers in making appropriate drug choices or assessing the quality of medication [6,7,8]. Explicit criteria, occasionally combined with other measures, are also used as tools to conduct medication reviews [9]. Since their introduction in 1991, the Beers criteria, and subsequently adapted sets (STOPP/START criteria) in various countries have been revised and refined with respect to structure and comprehensiveness [7,10].

In order to detect DRPs and optimize treatment, primary caregivers should periodically review the medication of older patients with chronic diseases [6,11-14]. Being the most comprehensive form of medication review [15], a clinical medication review (CMR) is a structured, critical examination of a patient's medications. Its objective is to reach an agreement with the patient about treatment, optimizing the impact of medicines, minimizing the number of DRPs and reducing waste [12-16].

Although a review of medication records solely on the basis of explicit criteria may be useful, the result in terms of detected DRPs will be of limited value since medical status, clinical parameters and the way patients experience their treatment have not been considered [11,13,15,17]. Therefore, only a medication review with direct input from the patient, addressing perceptions of convenience and effectiveness of treatment and eventual discomfort due to adverse events. In this way, treatment can be continued in an effective, satisfactory and safe manner [11,15,17,18]. This more clinical approach to the medication review, however, requires expert judgement and is likely to be time consuming [6,13]. Due to its comprehensive nature, the large input of data and involvement of the general practitioners (GPs), pharmacist and patient, the review process must be highly structured in order to be both cost-effective and practicable [11,13]. The availability of a tool to be used for the gathering of medication data and DRPs and their evaluation within

the framework of a CMR process essentially similar to that described and used by Lowe and colleagues, would be very helpful in implementing CMR in daily practice [12,15].

The aim of the present study was therefore to develop a structured, comprehensive, but practicable tool to facilitate and support the periodic review of older patients' medication by community pharmacists and GPs. The tool accounts for the perspective of the patient.

RESEARCH DESIGN AND METHODS

The present medication review tool is focused on the most commonly occurring chronic diseases in older persons, 65 years or older, in the Netherlands as listed by the National Institute for Public Health and Environment [19] and the medicines most frequently used to treat these disorders as listed each year by the Dutch Foundation for Pharmaceutical Statistics [20].

In the Netherlands, in primary care older patients with a chronic disease are generally treated according to the recommendations of the Dutch GP treatment guidelines [21].

With respect to criteria for appropriate prescribing and the design and implementation of a CMR, PubMed and the Cochrane library were searched using the following search terms: 'development', 'tools', 'method', 'medication review', 'clinical medication review', 'drug related problems', 'inappropriate medicines', 'inappropriate prescribing', 'explicit criteria', 'adverse effect', 'side effect', 'drug-drug interaction' and 'older patients'. Only full-text papers in English and Dutch up to December 2012 were included. Reference lists of identified research papers were also checked.

On the basis of the references and literature data and their clinical experience two authors in their capacity as community-pharmacist/clinical pharmacologist (JGH) and clinical pharmacologist/GP (PE) compiled a longlist of frequently occurring DRPs in older patients with a chronic disease. Medication recommended by the Dutch GP (NHG) treatment guidelines was considered appropriate, deviations were considered inappropriate. DRPs definitions were extracted from the PCNE DRP classification document (version 6.2) [3]. The PCNE classification and the list of patient-related DRPs compiled by De Smet et al. [11] were used to formulate a number of questions related to patient perceptions of drug treatment. Questions were organized in the form of a script for a structured patient interview. Data gathered during the interviews should be used to complete the DRP checklist. Results of studies on the occurrence of DRPs in older patients were used to check the DRP checklist [5,22-25].

The CMR tool consisting of a DRP checklist and interview script was optimized stepwise by means of a Delphi procedure of two rounds with a panel of eleven experts in the field and actual testing.

The experts in the field included (clinical) pharmacists, clinical pharmacologists, geriatricians and GPs with cardiovascular, asthma/COPD, diabetes or osteoporosis expertise. The panel was asked to comment on the longlist and interview script. Panel members were invited to add, change or delete items if they felt it necessary. All changes proposed were discussed by the authors. If the majority thought a change would be useful, the change was made definitive.

The CMR tool was used in a randomized controlled trial to evaluate the effect of a CMR and patient counseling on DRPs and compliance after hospital discharge [26,27]. Using medication records, medical and patient data, the tool was manually applied in this study. On the basis of trial experiences the tool was re-evaluated with the authors of this study and several suggestions for improvement were put forward. Subsequently, in the second Delphi round, the members of the expert panel were asked to comment on the resulting tool in a similar fashion to the first Delphi round.

RESULTS

The CMR tool comprises a comprehensive checklist of drug and patient related DRPs and a script for structured patient interviews aimed at identifying DRPs related to patient experiences with drug treatment for chronic diseases.

The checklist

The checklist consisted of domains. Of the ten most frequently occurring chronic disorders in Dutch older patients visual disturbances (nr. 1) and deafness (nr. 5) were excluded. Since cancer treatment is given predominantly to hospitalized patients or is hospital-directed, DRPs directly related to anti-cancer treatment were also excluded. Based on the remaining seven chronic diseases, the medicines most frequently used to treat these disorders and a number of patient-related issues related to the physiological system were included. Domains were ordered into 20 sections. DRPs cover both PIM and omissions of potentially beneficial pharmacotherapy. Where appropriate, DRPs also relate to laboratory values including glucose and HbA1c levels, blood pressure and lipoprotein levels.

The resulting tool consisted of a longlist consisting of 76 DRPs. After the first Delphi round, the list increased to 126 DRPs. Examples of DRPs that were added were: 'use of high dose of metformin and modification of diet in renal diseases (MDRD) < 30 ml/min' and 'no antihypertensive medication in the presence of micro-vascular complications'. After this Delphi round the tool was used in a randomized controlled trial with 340 older patients discharged from the hospital [26].

In the second Delphi round, three DRPs were deleted from the longlist and one DRP was added. The final list consisted of 124 DRPs ordered into 11 domains and 20 sections (Appendix 1).

The interview script

The interview script consisted of 5 sections including 34 questions addressing items such as the perceived effectiveness of medicines, side effects, problems with the taking of medicines and problems with respect to adherence (Appendix 2).

DISCUSSION

The present study concerns the development of a structured and comprehensive tool to facilitate and support (community) pharmacists in conducting a CMR of older patients with chronic diseases in close co-operation with the patient's GP. The CMR tool consists of a checklist of 124 common DRPs and a script for structured patient interviews used for the identification of patient-related DRPs.

In addition to several drugs-to-avoid and criteria addressing omissions of potentially beneficial medicines, the present structured list of DRPs includes important drug-drug and drug-disease interactions, dosing issues and duplicate prescriptions. With respect to these drug and disease-related items there is overlap with existing lists of explicit criteria developed to identify PIM like the Beers list, STOPP/START and the PRISCUS criteria. However, the Amsterdam Tool differs from these instruments (with the exception of STOPP/START) by being based on DRPs rather than on drugs and diseases and by containing criteria of medicine use based on laboratory values. However, most importantly the tool addresses DRPs from the patient's perspective. Lists of explicit criteria have not been developed as instruments to support caregivers in conducting a CMR. Nevertheless, in the Netherlands, a Multidisciplinary Guideline for Polypharmacy (MDG) has recently been developed [12]. As an elaboration of the MDG for polypharmacy, STOPP/START criteria were recently translated into Dutch and supplemented by a step-by-step procedure for the performance of a CMR under the name 'STRIP method' [12,28]. The 'Amsterdam Tool for Clinical Medication Review' can be used as an supplement to these and other methods for medication review. Many older patients with a chronic disease require specialist treatment and their hospitalization rate is well above average [6]. However, care is predominantly provided by GPs whereas medicines are supplied by community pharmacists. In the Netherlands, most patients obtain their medicines from the same pharmacy [6,29]. Electronic pharmacy medication records (PMR) are therefore fairly complete and usually also include data on hospital prescriptions [29].

The PMR are therefore an excellent starting point for a CMR and the data contained therein are the main substrate for checking for DRPs and the subsequent evaluation. PMR, however, must be

combined with medical record data provided by the GP [12]. However, in spite of the considerable amount of expert knowledge already present, additional training with respect to (geriatric) pharmacotherapy and improvement of communication skills in order to conduct structured patient interviews may be required. In this respect, studies in Finland and New Zealand suggested that health care professionals did not possess the competences to conduct a CMR [16,30].

A strength of the screening of medication using explicit criteria in the form of the CMR tool is a process that takes relatively little time to perform. On the other hand, the patient interview required to obtain information on DRPs from the patient's perspective, the evaluation of the medication data and patient experiences in collaboration with the GP and the subsequent transfer of information to the patient and counseling are time consuming. Time consumption is also highly variable since it depends on wide variety of patient-related factors. Any measure to make a CMR more time efficient is therefore extremely useful.

Using the structured interview script will also increase the quality of the initial interview with the patient. The present tool is therefore an important contribution in terms of enhancing the efficiency of the CMR process and makes it more applicable in practice. The Amsterdam Tool for Medication Review has been used in a randomized controlled study of the effect of a CMR on the incidence of DRPs among 340 older patients discharged from the hospital [26]. In this study, the CMR resulted in a significant reduction in DRPs among patients. In particular, the DRPs 'no drug but clear indication' and 'fear for side effects' were significantly reduced. Subgroup analyses showed that the reduction of DRPs identified with medication analysis was significantly more pronounced among patients with hypertension ($p=0.011$) and heart failure ($p=0.001$) [26]. The results obtained with the preliminary version of the tool indicate that the application of the tool in the CMR process was effective and considered practicable.

The tool was developed on the basis of data obtained by means of a literature search on the subject of CMR and DRPs, clinical expertise and a Delphi procedure. Experts were asked to appraise the initial tool with respect to completeness, accuracy and redundancies. A limitation of our study was the lack of validation of the CMR tool. The CMR tool was tested in a randomized controlled study, but further validation is necessary. Another limitation is the rapidly change in demographic pattern of diseases, evidence-based therapies & guidelines in the different countries. Therefore periodically revising the contents of the CMR tool will be necessary. The panel of experts did not include a mental health person. Given the extent of mental health issues in the elderly, a mental health person could give useful suggestions.

In conclusion, we developed a structured, comprehensive and practicable tool for pharmacists and GPs to perform CMR, including a list of potential DRPs in older patients with chronic disease

and a script for structured patient interviews. Future studies should address the implementation of this tool in daily practice, particularly with respect to electronic DRP screening and improving the interaction of electronic pharmacy and GP information systems in order to enhance the efficiency at the evaluation and communication stages. In addition, the effects of using the tool in CMR processes on health outcomes and costs should be investigated.

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APPENDIX 1

Checklist of (potentially) drug-related problems (DRP) in older patients with a chronic disease.

Introduction

This is a checklist of (potentially) DRP which a pharmacist in close cooperation with the general practitioner (GP) should recognize using the medication status of the patient and the result of a patient interview.

A. Cardiovascular diseases

Hypertension

DRP based on medication status:

1. Use of Beta - blockers in combination with or non-steroidal anti-inflammatory drugs (NSAIDs) in high dose [1,2].
2. Use of more than three antihypertensive in combination with a NSAID.
3. Use of antihypertensive drugs of which the cardiovascular outcomes are not evidence-based (prazosin, doxazosin and methyl dopa).

DRP related to medical status:

4. Antihypertensive treatment does not result in a systolic blood pressure < 140 mmHg.
5. Treatment with an antihypertensive, but without regular assessment of creatinine and potassium blood levels in patients having renal dysfunctions and using diuretics, ACE inhibitors or angiotensin II antagonists [3].
6. Hypertension as a result of renal insufficiency, treated with antihypertensive medication [1].

Angina pectoris

DRP based on medication status:

7. No use of acetylsalicylic acid (80 mg) as secondary prevention of heart disease.
8. Use of acetylsalicylic acid in combination with NSAID and no use of a stomach protector^a [4].
9. Use of acetylsalicylic acid in combination with selective serotonin reuptake inhibitor(SSRI) and no use of a stomach protector^a [4].
10. Use of clopidogrel in combination with omeprazol or esomeprazole^b [5,6].
11. Use of sildenafil in combination with nitrates (before 24 hours)^c [7].
12. Use of too much nitro-glycerine sprays (overuse).
13. Use of short-acting nifedipin capsules [8].

DRP related to medical status:

14. Target value of 50 to 60 beats per minute under maintenance treatment not achieved.

Cardiovascular diseases including myocardial infarction, angina pectoris, stroke,transient ischemic attack (TIA), aorta aneurysm and peripheral arterial disease

DRP based on medication status:

15. The statin dose is too low or a statin is not prescribed (first choice is simvastatin or pravastatin 40 mg)^d [3].
16. No use of acetylsalicylic acid (80 mg) or other antiplatelet drug as secondary prevention of heart disease.

DRPs related to medical status:

17. LDL > 2.5 mmol/L [9].
18. Systolic blood pressure is > 160 mmHg but antihypertensives have not been prescribed.
19. Use of amiodaron in combination with thyroid dysfunction [10].

Atrial fibrillation

DRP based on medication status:

20. Use of a beta blocker in combination with verapamil/diltiazem^e.
21. Rise of the digoxin level due to an interaction with verapamil (to a lesser extent also with diltiazem) and amiodaron.
22. Coumarin derivative not used, in spite of a clear indication on the basis of the Chads criteria and absence of a contra-indication for a coumarine (frequent falls, low adherence).
23. Use of digoxin and/or verapamil and/or a beta blocker in combination with sotalol, amiodaron or a class I anti-arrhythmic.

DRP related to medical status:

24. Digoxin level not monitored.
25. Serum potassium levels not monitored.
26. Heart rate is 70 – 90 beats per minute in rest or more than 110 beats per minute during light exercise.

Systolic heart failure

DRP based on medication status:

27. Treatment with a diuretic absent.
28. Treatment with a renin-angiotensin system (RAS) –inhibitor absent.
29. Presence of tickling cough due to treatment with an ACE-inhibitor [3].
30. Use of verapamil [11].
31. Use of diltiazem or verapamil without concomitant use of digoxin.
32. Chronic use of NSAIDs [12].

33. Use of NSAIDs in combination with a high dose of a loop diuretic (furosemide, bumetanide) or in combination with a sodium eliminating diuretic (hydrochlorothiazide) [13].
34. Use of a thiazide without concomitant use of a loop diuretic in spite of renal function impairment (creatinine clearance < 30 ml/min).
35. Statin treatment absent in spite of diagnosed heart disease and LDL > 2.5 mmol/L [3].
36. Statin dose too low (first choice is simvastatin or pravastatin 40 mg)^d [3].
37. Beta blocker (carvedilol, metoprolol or bisoprolol) not used.
38. Spironolactone not used in spite of New York Heart Association (NYHA) class II or III heart failure with reasonable renal function.
39. Combined use of an ACE-inhibitor and an AT1 antagonist [14].
40. Use of diuretics for static oedema but heart failure not diagnosed.
41. Ankle oedema due to calcium channel blocker use but heart failure not diagnosed.
42. Reconsider the indication for thiazides if there is a diagnosis of gout [15].

DRP related to medical status:

43. Heart failure diagnosed but NYHA classification not applied.
44. Renal function has not been assessed in the previous calendar year.

Anticoagulant use (use related to heart disease or stroke prevention)

DRP based on medication status:

45. Despite application of therapeutic index range for coumarin treatment (2.0-2.5), the target value of the internationalized normalized ratio (INR) of 2.5 is not reached [16].
46. Absence of gastric acid protection in patients ≥ 70 years of age.
47. No clear indication for the use of a coumarin in combination with acetylsalicylic acid and/or clopidogrel.
48. Use of the combination of a coumarin and acetylsalicylic acid in the absence of gastric acid protection.

DRP related to medical status:

49. INR incorrectly set at a value < 2 or > 3.
50. Combination of a coumarin with a platelet aggregation inhibitor not indicated.

B. Artrose and rheumatic diseases

DRP based on medication status:

51. Renal failure diagnosed.
52. Acetylsalicylic acid use in combination with a NSAID, without use of a stomach protector^a [4].
53. Acetylsalicylic acid use in combination with a SSRI, without use of a stomach protector^a [4].
54. Use of NSAIDs without stomach protection in patients ≥ 65 years of age.

DRP related to medical status:

- 55. Use of NSAID, although an alternative is possible, like paracetamol.

C. Type 2 Diabetes Mellitus

DRP based on medication status:

- 56. No use of metformin^f [17].
- 57. Use of glibenclamide and frequent occurrence of episodes of hypoglycaemia [18].
- 58. Use of pioglitazone in combination with a loop diuretic^g [19].
- 59. Use of hypoglycaemic agents in combination with non-selective beta blockers (except sotalol).
- 60. Statin dose too low (first choice is simvastatin or pravastatin 40 mg)^d [3].
- 61. Concomitant use of medicines potentially disturbing blood glucose levels, e.g. high dosed thiazides (> 12.5 mg/day) or corticosteroids (prednisone > 7.5 mg/day) [20].
- 62. Use of calcium channel blocker as sole antihypertensive medication.

DRP related to medical status:

- 63. Fasting glucose level in venous plasma is not between 4.5 – 8 mmol/L.
- 64. Frequent occurrence of hypoglycaemic episodes.
- 65. Glycosylated haemoglobin (HbA1c) > 69 mmol/L (8.5%).
- 66. Systolic blood pressure > 140 mmHg but antihypertensive treatment absent.
- 67. No use of statin in case of low-density lipoproteins (LDL) > 2.5 mmol/L or total cholesterol (TC) > 4.5 mmol/L [17].
- 68. Presence of (micro-) albuminuria but treatment with an angiotensin-converting enzyme (ACE) -inhibitor (or angiotensin II receptor type 1 (AT1) -antagonist) absent [21].
- 69. Oedema is reported in combination with the use of pioglitazone.
- 70. Use of high dose of metformin and modification of diet in renal diseases (MDRD) < 30 ml/min [17].
- 71. No antihypertensive medication in the presence of micro-vascular complications.
- 72. No periodic assessment (once yearly) of renal function, HbA1c, blood pressure and urinary micro-albuminuria.

D. Asthma / COPD

DRP based on medication status:

- 73. Daily dose of beta-sympathomimetic higher than maximum dose^h [22].
- 74. Daily dose of inhalation corticosteroid higher than maximum dose.
- 75. Use of a beta blocker and/or timolol eye drops in spite of severe asthma statusⁱ [23].
- 76. Use of long acting beta -2 agonists (salmeterol) as 'if necessary'.
- 77. Use of inhalation corticosteroid as 'if necessary'.

DRP related to medical status:

- 78. Disease status according to the Chronic Respiratory Disease Questionnaire (CRDQ) unknown?
- 79. The clinical status of the patient is not stable, but sharply fluctuating.
- 80. Frequent episodes of oral corticosteroids use (possible sign of compliance problems).

E. Severe pain

DRP based on medication status:

- 81. Use of opioids without use of laxative.

F. Osteoporosis

DRP based on medication status:

- 82. Supplementary calcium and/or vitamin D not prescribed while indicated.
- 83. Use of biphosphonate or denosumab without calcium and vitamin D supplementation^j.
- 84. No use of biphosphonate and no use of it previously for a maximum period of five years.
- 85. Chronic use of highly-dosed (> 7.5 mg/day) prednisolone or equivalent without concomitant use of a biphosphonate or denosumab.
- 86. Use of etidronate^k [24].
- 87. Biphosphonate not taken on an empty stomach.
- 88. Simultaneous use of a biphosphonate and a Ca-, Al-, Mg-, Fe- or Zn- containing drug.
- 89. Severe decrease of renal function (GFR < 30 ml/min) and no use of vitamin D.
- 90. Use of active vitamin D metabolites in primary care setting.

G. Disorders of the central nervous system

Depression

DRP based on medication status:

- 91. Use of an incorrectly-dosed antidepressant [25].
- 92. Duration of treatment with an SSRI too short (< 4 weeks)ⁱ [25].
- 93. Use of SSRI longer than six months after a single episode of depression [25].

- 94. Use of a tricyclic antidepressant as a first choice in depression in the presence of cardiovascular risk factors or cardiovascular disease^m.
- 95. Use of a tricyclic antidepressant in spite of a history of glaucoma, orthostatic hypertension or bladder retention^m.
- 96. Use of a SSRI in spite of a history of hyponatremiaⁿ.

DRP related to medical status:

- 97. Continued treatment for depression in spite of lacking indication.
- 98. Discontinuation of antidepressant, which leads to withdrawal symptoms [26].

Sleep disorders

DRP based on medication status:

- 99. Use of other benzodiazepines than temazepam or zolpidem.
- 100. Hypnotic medication is used chronically and not intermittent.
- 101. Benzodiazepine dosage is too high.

DRP related to medical status:

- 102. Chronic benzodiazepine use without indication for sedation or anxiolysis at daytime.

H. Disorders of the central nervous system related to cognitive function

Psychiatric disorders

DRP based on medication status:

- 103. Use of lithium without monitoring of lithium blood level, renal function, minerals (calcium, magnesium), thyroid function.
- 104. Unnecessary or ineffective use of anticholinergic medication (oxybutinine, solifenacine, tolteridone and promethazine).
- 105. No periodic evaluation of antipsychotic drug use.

Parkinson's disease

DRP based on medication status:

- 106. Use of other antipsychotics than clozapine and quetiapineⁿ.

DRP related to a medical problem:

- 107. Use of clozapine without monitoring of white blood countⁿ.
- 108. Disease symptoms related to the use of neuroleptics, SSRI or metoclopramide?

I. Gastrointestinal disorders

Stomach disorder

DRP related to medical status:

- 109. Indication for treatment with an acid inhibitor no longer present but treatment continued.

Constipation

DRP based on medication status:

- 110. Unnecessary and/or prolonged use of laxatives.
- 111. Use of codeine as prescribed for pain or coughing complaints.
- 112. Use of Fe supplementation without a clear indication.

J. Older patients dependent on home care or in nursing homes

DRP based on medication status:

- 113. Medication associated with a higher risk of fall incidents (i.e. benzodiazepines, antidepressants, antipsychotics and cardiovascular medicines).
- 114. Use of medication with a higher risk on decline of cognition (i.e. antipsychotics and anticholinergics).

L. Other problems related to the medication status

- 115. Double medication is reported.
- 116. The indication for the drug is unknown
- 117. Relevant drug interactions and contra-indications are identified based on the pharmacy/GP computer information system.
- 118. Medication record suggesting non-adherence.

K. DRP related to the perspective of the patient

- 119. Treatment indication unknown to the patient.
- 120. Absence of awareness how to use medication.
- 121. Dissatisfaction about the medication (medication as such or effectiveness of medication).
- 122. No trust in or doubts about the effectiveness of the medication.
- 123. Patient experiences adverse drug event(s).
- 124. Fear for adverse drug events.

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APPENDIX 2

Script for patient interview (*provides information for part 'DRPs related to the patient' of the checklist*)

1. Preparing the interview:

- Which chronic medicines is the patient using according to the pharmacy information system?

2. Start of the interview:

- Which medicines are you using?
- Are you using other medicines than prescribed by the general practitioner/specialist, like painkillers or vitamins?
- Is someone helping you with the management of your medicines?

3. Effectiveness of the medicines:

- Do you know for what disease or symptom you have to use your medicine?
- Is your medicine effective?
- Why do you think your medicine is effective or not?
- Do you know when to take your medicine, like before/after a meal or before sleeping?
- Do you know how to use your medicine?

4. Adverse drug effects of the medicines:

- Are you experience adverse drug effects of your medicines?
- Of which medicine do you experience an adverse drug event?
- Which adverse drug event do you experience?
- How long do you experience this adverse effect?
- Are you afraid to experience adverse drug effects of your medicines?
- Of which medicine are you afraid to experience adverse drug effects from?
- For which adverse drug effect you are afraid?
- Have you, once or more, been fallen in the past year?

5. Problems with the use of the medicines:

- Do you sometimes forget to use your medicine?
- Which medicine do you sometimes forget to use?
- What was the reason you forget to use the medicine?
- Do you have a method which remembers you to use your medicines?
- Do you sometimes consciously not use your medicines?
- Which medicine are you sometimes consciously not using?
- What is the reason you sometimes consciously not use the medicine?

- Have you ever stopped using your medicine on your own initiative?
- With which medicine you stopped on your own initiative?
- What was the reason you stopped the medicine on your own initiative?
- Is it difficult for you to take your medicines?
- Which medicine is difficult to take?
- Why is it difficult for you to take this medicine?
- Are you getting help with the use of your medicines?
- What kind of help did you get with the use of your medicines?
- Would you, if possible, use a combination drug?
- Are you generally satisfied with your medicines?

Thank you for your time.

Chapter 9

General Discussion



The principal aim of this thesis was to reach a greater understanding in treatment goals and the effectiveness of current treatment strategies in glycemic control in people with Type 2 Diabetes Mellitus (T2DM) in daily practice. Additionally, the evaluation of an intervention to improve patient involvement and the development of an intervention to optimize T2DM treatment was investigated. Overall, the present thesis should contribute to the optimization of treatment strategies and personalization of treatment goals in people with T2DM.

In this final chapter the main findings of the previous chapters will be reviewed in the context of the current literature. Methodological issues, future perspectives and the role of the community pharmacist in T2DM management will also be discussed.

TREATMENT GOALS AND EFFECTIVENESS OF TREATMENT STRATEGIES ON GLYCEMIC CONTROL IN T2DM

Guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend target HbA1c values of ≤ 53 mmol/mol (7.0%) in the majority of the people with T2DM [1,2]. Not reaching the target HbA1c values of ≤ 53 mmol/mol (7.0%) has been shown to increase the risk of diabetes related complications [3-5]). Treatment of people with T2DM initially involves lifestyle changes and therapy with oral glucose lowering agents. In case of an inadequate response to oral glucose lowering agents, treatment with insulin is indicated [1,2,6]. In chapter 2, we described that most people with T2DM (61%) in the Hoorn Diabetes Care System Cohort, who were initially treated with oral glucose lowering agents initiated insulin during follow-up (mean follow up 5.4 years, SD 3.4). Preceding the initiation of insulin, people with T2DM were mainly treated with metformin and/ or a sulphonylurea (SU) derivate. The literature showed a proportion varying from 40-60% of patients that initiated insulin and a time to insulin initiation varying from 2-8 years. In our cohort, the time to insulin initiation was rather short, ranging from a median time of 1.2 years in people with HbA1c levels consistently ≥ 53 mmol/mol (7.0%) to 5.4 years in people with fluctuating HbA1c levels around 53 mmol/mol (7.0%). Longer diabetes duration and a lower age at baseline were associated with a shorter time to insulin initiation. This study provide proof that managed diabetes care through a central organization resulted in a short time to insulin initiation.

In chapter 3, the effectiveness of insulin therapy on glycemic control was evaluated using Latent Class Growth Modelling, an advanced statistical technique. The study population comprised 1,203 people with T2DM of the Hoorn Diabetes Care System Cohort who initiated insulin (mean follow-up 5.6 years, SD 2.8). With Latent Class Growth Modelling, four HbA1c trajectories could be distinguished. The trajectory containing the majority of people (88.7%) comprised those who had stable HbA1c levels during follow up of around 57 mmol/mol (7.4%). Another trajectory

(3.9%) consisted of people who had very high HbA1c levels of 95 mmol/mol (10.8%) at initiation of insulin, which gradually decreased to 73 mmol/mol (8.8%) over a 10 year period. The smallest trajectory (3.0%) consisted of people with a steadily increasing HbA1c from a baseline level of 65 mmol/mol (8.1%), to 92 mmol/mol (10.6%), following the initiation of insulin therapy. The final trajectory (4.4%) consisted of people who had high HbA1c levels starting at 85 mmol/mol (9.9%) that decreased within the first three years to around target levels of 51 mmol/mol (6.8%).

To analyse the sustainability of the HbA1c levels over time, the proportion of people with T2DM who were 'off-target' and 'on-target' was calculated. These data showed us that of the 1,203 people initiating insulin therapy, 24.4% were 'on-target' during the total follow-up of 5.5 year, whereas 75.6% stayed 'off-target'. People in the 'off-target' group were significantly younger and had higher HbA1c and glucose levels at the initiation of insulin. Overall, these findings show that initiating insulin earlier improves the likelihood of achieving and sustaining glycemic control.

In chapter 4, using the same Latent Class Growth Modelling analysis technique, we defined subgroups of HbA1c trajectories in the Hoorn Diabetes Care System Cohort ($n = 5,423$, mean follow up 5.7 years, SD 2.3). Again, four subgroups were defined: (1) the largest group (83.1%) with people who maintained HbA1c levels around 53 mmol/mol (7.0%) during follow up; (2) a subgroup (8.2%), who initially showed severe hyperglycaemia, but reached the recommended HbA1c targets within two years; (3) a subgroup (5.2%) with people who showed hyperglycaemia and did not reach the recommended HbA1c target; (4) the smallest subgroup (3.4%), people with deteriorating hyperglycemia over time. People within the largest group (83.1%) and second subgroup (8.2%) mainly used metformin and a SU-derivate during follow up. People in the smallest subgroup more frequently initiate insulin during follow up. The people in the last two subgroups were significantly younger, had higher HbA1c levels and a longer diabetes duration at baseline. This study provides proof that most people with T2DM within our study population were well controlled.

EFFECTIVENESS OF TREATMENT STRATEGIES ON CO-MORBIDITIES IN T2DM

Hypertension

In addition to HbA1c treatment goals, the ADA and EASD provide treatment goals for systolic blood pressure (SBP). Untreated or poorly controlled hypertension in people with T2DM has an additional effect on cardiovascular risk and micro and macro vascular complications [7,8]. Identifying subgroups of people with T2DM with distinct trajectories of blood pressure levels is important in order to eventually improve their medication management. Therefore, in chapter 5, subgroups of people in the Hoorn Diabetes Care System Cohort with a distinct SBP course over time were

identified using Latent Class Growth Modelling ($n = 5,711$, follow up time 5.7 years, SD 2.3). The largest subgroup (85.6%) showed adequate SBP levels around 140 mmHg over time. A second subgroup (5.6%) consisted of people who were hypertensive in the first five years, and who responded slowly to antihypertensive management. The third group (3.4%) showed deteriorating hypertension during the first four years, then showed insufficient response to antihypertensive management. The last subgroup (5.4%) showed deteriorating hypertension during follow up. People with T2DM in subgroup 2-4 were significantly using more antihypertensive medication than those in group 1 with adequate SBP levels. Overall, this suggests that, under the current guidelines, long-term SBP control is still suboptimal in people with T2DM treated within primary care. Even though more than 85% of the people with T2DM reached and maintained stable SBP levels at or around 140 mmHg during an average of 5.7 years of follow-up, classes with a more unfavorable course of SBP control showed higher rates of complications.

Depression

With depression being present in approximately 20% of people with T2DM, which has a role in glycaemic control [9-12], we expect equally frequent prescriptions of antidepressants, anxiolytics and hypnotics. In chapter 6, the use of antidepressants, anxiolytics and hypnotics in people with T2DM and socio-demographic characteristics of users and non-users in people with T2DM from the Hoorn Diabetes Care System Cohort was assessed ($n=7,016$). We observed that 7.1% used antidepressants only, 6.5% used anxiolytics and/or hypnotics only and 3.6% used drugs of both categories. As expected, antidepressants, anxiolytics and/or hypnotics use was slightly higher in people with T2DM, compared to the general population in which 6% is prescribed antidepressants and 7.5-9.9% anxiolytics and hypnotics [9,13]. No differences in co-morbidities and HbA1c levels were observed between users and non-users. However, users were more frequently treated with insulin.

INTERVENTIONS TO IMPROVE PATIENT INVOLVEMENT AND EVALUATE TREATMENT STRATEGIES

In addition to adjusting medication use, another way to improve health is by enhancing the involvement of people with T2DM in their treatment [14-18]. For this purpose a web-based guided insulin self-titration program was developed. Chapter 7 concerns the evaluation of the feasibility of the web-based guided insulin self-titration program in people with T2DM treated by the primary care physician. People with T2DM adopted a web-based insulin-titration self-management program, while Primary Care Physicians (PCPs) indicated no needs for the program. The lesson to be learned was to investigate the potential barriers that all stakeholders may face *before* implementing an e-health program in order to a) try to embed and tailor a program to the care setting b) decide on (not) to implement if doubts exist about embedding or need is lacking.

Finally, people with T2DM are often experiencing drug related problems due to the high number of medications. These drug related problems substantially increase the risk of morbidity, hospitalisation and mortality [19,20]. To identify drug related problems and optimize treatment PCPs and pharmacists should periodically review the medication of people with T2DM. Therefore, we described in chapter 8 the development of a structured and comprehensive tool to facilitate and support community pharmacists in conducting a clinical medication review. The medication review tool consists of a comprehensive checklist of 124 drug-related problems divided by 20 sections according to physiological systems and diseases, and includes a script for a structured patient interview.

METHODOLOGICAL CONSIDERATIONS

The studies described in chapters 2 – 5 and chapter 7 were conducted in people with T2DM participating in the Hoorn Diabetes Care System, a centrally organised managed diabetes care system, in which a strict treatment protocol [21] is applied by all caregivers in this region. Therefore, this cohort is not representative for diabetes care in other regions of the Netherlands and other western countries. However, the cohort provided optimal conditions to address the research questions of chapter 2-5 and 7. It will be of great interest to perform similar studies in another treatment setting, for example less strictly controlled, primary care settings or secondary and tertiary care.

Several strengths and weaknesses of the reported study need to be acknowledged in order to enable a proper interpretation of the results.

A limitation of an observational cohort study is missing follow-up data. However, since the treatment protocol is strictly applied and data are accurately registered the number of missing values in our cohort is very small. In the chapters of this thesis a variety of statistical methods to deal with missing data were used. In chapter 2 we used Cox-regression analysis, in which the missing data of people with T2DM is taken into account. In chapters 3-5 the Latent Class Growth Modelling technique was used with the assumption that missing data are missing at random, and therefore do not influence the analysis. A limitation of the study on the feasibility of a web-based insulin titration program presented in chapter 7 is that not all participating primary care physicians were interviewed by telephone. Therefore it is possible that not all reasons for not implementing the web-based insulin-titration self-management program have been collected. However, to overcome this limitation and to get insight into the opinion of PCPs on the implementation of the web-based insulin-titration self-management program, we performed a focus-group discussion.

A strength is the observational character of the study with a long term follow up (up to ten years) in a population-based diabetes cohort with standardized yearly measurements and therefore completeness of the dataset. While most of the ADA/ EASD and NHG guidelines on treatment strategies among people with T2DM are generally based on results from randomised clinical trials (RCTs), observational research is an important complementary approach employed to document the use of drugs in daily clinical practice. RCTs have their limitations (due to the use of exclusion criteria) as they are often conducted in relatively healthy people with T2DM under strictly controlled circumstances with a short follow up. Therefore, results of the observational studies described in the present thesis are important, because the people with T2DM in daily practice differ from the people that have been included in RCTs.

FUTURE PERSPECTIVES, TOWARDS A PATIENT-CENTERED APPROACH

Based on the research presented in this thesis, the following recommendations can be made to further improve diabetes care and to enhance personalized medication use.

Implementation of centrally managed diabetes care In this thesis, we showed that managed diabetes care [8,21] through a central organization results in the majority of the people with T2DM in HbA1c levels around 53 mmol/mol (7.0%) and adequate SBP control with levels of < 140 mmHg. Possibly due to the centrally managed diabetes care (chapter 2), the time to insulin initiation is short (median 1.2 years) compared to existing literature [22-24]. Implementation of managed diabetes care appears successful in improving treatment targets and treatment strategies in people with T2DM and should be implemented in other regions of the Netherlands. However, a small group of people with T2DM have insufficient glycemic and blood pressure control, even in centrally organized diabetes care. For those people, the current guidelines might not provide the best treatment and more personalized care strategies may be required.

Earlier initiation of insulin People with T2DM with a short duration of diabetes and people not responding to oral glucose lowering agents benefit from early initiation of insulin (chapter 3). Moreover, we showed that initiation of insulin did not lead to adequate glycemic control in people with a long diabetes duration and long history of high HbA1c levels. These findings are in accordance with the literature [25-27]. Previous studies [28-31], showed that a lower HbA1c level at the start of insulin treatment was associated with a higher likelihood of reaching the HbA1c targets, which is also in agreement with our findings. Early initiation of insulin slowed the progression of diabetes and reduced the risk of long-term complications through preservation of remaining beta-cell function and improvement of the metabolic memory [3-5,25,32]. One of the explanations of the metabolic memory is characterized by accumulation of the substance AGEs, which is formed during periods of hyperglycemia. Accumulation of AGEs leads to vascular

stiffness and thereby induced micro and macro vascular complications [33]. Despite growing evidence on the favorable effects of early insulin initiation there is still much discussion on the optimal timing of initiation of insulin.

Attention for hypoglycemia The subgroup of people with T2DM who had very high HbA1c levels at the initiation of insulin and a fast decrease in HbA1c levels, showed a higher mortality as compared to the other subgroups, despite similar baseline parameters (chapter 3). The higher mortality rate might be explained by a higher risk of hypoglycaemia. The higher mortality rate is in concordance with the results from the ACCORD study, the Veterans Affairs Trial and the General Practice Research Database [34-36]. The subgroup with poor HbA1c levels at baseline, but with a less rapid reduction in HbA1c during follow up was not associated with excess of mortality. Therefore, it seems important to avoid hypoglycemic events.

More attention for younger people with T2DM Younger age was associated with an unfavorable course of glycemic control over time and a higher risk of micro vascular complications within the same follow up period compared to people with a higher age (chapters 3 and 4). Our results are in concordance with The Action in Diabetes and Vascular Disease (ADVANCE) trial, which demonstrated a higher risk of micro vascular complications in the younger people with T2DM [37]. It might be possible that younger people with T2DM have another type of T2DM resulting in worse glycemic control and more micro vascular complications. Therefore, more attention for people with T2DM who are younger is needed and stringent treatment goals are advisable.

EXPANDING THE ROLE OF THE COMMUNITY PHARMACIST IN T2DM CARE

We have shown that centrally managed diabetes care leads to clinical care outcomes and glycemic control that are better than those in other T2DM cohorts [2,3,22]. At present, diabetes care is predominantly provided by PCPs and diabetes nurses. PCPs who are currently in charge of primary diabetes care, struggle with medication management in T2DM. Nurses and non-specialized physicians were more reluctant to initiate insulin in a timely manner, compared to physicians specialized in diabetes [38]. A lack of expertise may account for this reluctance [38]. Moreover, the PCPs interviewed in the Di@log study reported that the initiation of insulin was difficult (Chapter 7). There seems to be a role for the community pharmacist in T2DM medication management: People with T2DM visit the community pharmacy often to discuss the perceptions of convenience and effectiveness of treatment and eventual discomfort due to adverse events, instead of visiting their PCPs practice.

Since medication play a pivotal role in the treatment of T2DM, people with T2DM frequently visit the pharmacy to fill their prescriptions. Thereby, pharmacy medication records are fairly complete

and include hospital prescriptions [39]. Community pharmacists therefore have the opportunity to provide adequate pharmaceutical care. In the past decade a shift from a product centered care to patient centered care has taken place in Dutch pharmacies and guidelines for pharmaceutical care for specific patient groups have been developed by the professional association of pharmacists. In order to warrant drug safety, at the initiation of therapy the pharmacist verifies drug choices and doses and checks for potential drug-drug interactions. In addition, the pharmacist should counsel people with T2DM about the action, side effects and use of the medicines in daily practice. It is known that people with T2DM who are better informed about their treatment are generally more adherent to the treatment with their medication, which results in improved treatment outcomes [40]. In addition, non-adherence with the use of medication can be identified by pharmacy information and administration system of the pharmacist. A recent systematic review of randomized controlled trials on the effectiveness of pharmacist interventions in the management of people with T2DM showed that pharmacist interventions indeed have a positive impact on clinical outcomes, like reduction in HbA1c, blood glucose, blood pressure, medication adherence and quality of life [40]. These findings support the involvement of a pharmacist in the integrated diabetes care team. To sum, given the expertise of the community pharmacist on medication safety and polypharmacy their role should be enlarged.

An example in which the pharmacist could play a role in improving medication safety is renal failure, because people with T2DM frequently have a decline in renal function, they are at greater risk of drug accumulation and as a consequence changes in doses can be necessary. Metformin for example, is contra-indicated in people with T2DM with a creatine clearance of less than 30 ml/min. In patients with a creatinine clearance of 30-50 ml/min the dose should be reduced to a maximum of 1.000 mg per day [41]. It is therefore important for pharmacists to have knowledge of the renal function of people with T2DM. The availability of LDL values, HbA1c values, and blood pressure values in the pharmacy is also mandatory. This would allow pharmacists to provide PCPs and nurse practitioners with tailored medication proposals for their people with T2DM, thereby contributing to an enhanced drug effectiveness.

People with T2DM often use multiple drugs to adequately treat their diabetes and associated comorbidities. Polypharmacy increases the risk of drug-related problems [42,43] which may increase the risks of morbidity, hospitalization and mortality [19,20]. To reduce the risk of drug-related problems and to increase drug appropriateness the medication of people with T2DM should regularly be reviewed by the PCP and the pharmacist.

A shared collection of pharmacy, laboratory and clinical data would facilitate the preparatory work for these type of pharmaceutical care activities.

Based on my research and my own experiences, I therefore believe that adding a pharmacist to the diabetes care team, will improve the medication safety and lower the polypharmacy problems, and work towards a patient-centered approach and reach high effectiveness of treatment strategies in T2DM.

THE FUTURE

Based on the current status of the field and the research presented in this thesis, there is a clear need for more observational research in order to unravel the causes underlying the existence of classes with suboptimal glycemic and SBP control within clinical practice. Eventually, this would improve glycemic and SBP control and thereby decrease the risk of complications in these patients.

A longer duration of diabetes and a younger age before initiation of T2DM management may benefit from tailored medication treatment strategies to achieve tailor-made glycemic control, and the effect of these advanced medication treatment strategies should be investigated.

Further it would be interesting to study the effect of antidepressants on the glycemic control and especially in people who initiated insulin. Finally, a pharmacist should be part of the multidisciplinary diabetes care team to enhance efficacy of treatment and to improve medication safety.

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Chapter 10

Summary

Nederlandse Samenvatting

List of publications

Dankwoord

Curriculum Vitae



SUMMARY

A general introduction on treatment goals and treatment strategies in diabetes mellitus is described in **chapter 1**. The aim of this thesis was to reach a greater understanding in treatment goals and effectiveness of treatment strategies on glycemic control in people with T2DM in daily practice. Secondly, the evaluation of an intervention to improve patient involvement was described. Finally, the development of an intervention to optimize diabetes treatment was described.

In the first part of this thesis (chapters 2 – 4), we focused on the treatment of T2DM in the real world.

In **chapter 2** we investigated the time to insulin initiation in people with T2DM not responding to oral glucose lowering agents and we evaluated long term outcomes, including glycaemic control, micro vascular complications and mortality. Our study demonstrated that two-third of the people with T2DM initiated insulin during follow up. The time to insulin varied from 1.2 years (range 0.3-3.1) in patients with HbA1c levels consistently ≥ 53 mmol/mol (7.0%) to 5.4 years (range 3.0-7.5) in patients with fluctuating HbA1c levels around 7.0%. Longer diabetes duration (HR1.04 95% CI 1.03-1.05) and lower age (HR1.00 95% CI 0.99-1.00) at baseline were associated with a shorter time to initiation. More insulin initiators had retinopathy compared to people with T2DM that remained on oral glucose lowering agents during follow up.

In **chapter 3** we described subgroups with distinct HbA1c trajectories in insulin users. We identified four HbA1c trajectories. Most people were classified in a stable HbA1c trajectory of around 57 mmol/mol (7.4%) (88.7%). Only 24.4% of the people were 'on-target' to insulin, this was associated with lower HbA1c levels and higher age at the start of insulin treatment. Initiating insulin earlier improves the likelihood of achieving and sustaining glycemic control.

In **chapter 4** we described subgroups with distinct HbA1c trajectories of the overall T2DM population. Four subgroups with distinct HbA1c trajectories were identified. More than 90% reached and maintained good glycemic control (subgroup one and two). Persons within the two subgroups that showed a more unfavorable course of glycemic control, were younger, had higher HbA1c levels and a longer diabetes duration at baseline.

The second part of this thesis focused on co-morbidities in T2DM management (chapters 5,6).

In **chapter 5** we investigated subgroups with distinct trajectories of systolic blood pressure in the overall T2M population. Four subgroups with distinct SBP trajectories were identified. The largest subgroup (85.6%) showed adequate SBP control (at or around 140 mmHg) over time. The second

subgroup (5.6%) were hypertensive in the first years, responded slowly to BP management and eventually reached SBP control. The third subgroup (3.4%) showed deteriorating hypertension during the first four years, then showed insufficient response to BP management. The fourth subgroup (5.4%) showed deteriorating hypertension over time. People with T2DM within subgroups 2-4 were significantly older, comprised more women, used more antihypertensive medication and had a higher prevalence of retinopathy, microalbuminuria and CVD mortality.

In **chapter 6** we described the use of antidepressants, anxiolytics and hypnotics in people with T2DM and determined the socio-demographic characteristics and T2DM medication associated with use. We demonstrated that from the 7,016 people with T2DM, 500 people (7.1%) used antidepressants only, 456 people (6.5%) used anxiolytics and/or hypnotics only and 254 people (3.6%) used a combination. Users were more often female, non-Caucasian and lower educated compared to non-users. Users of anxiolytics and/or hypnotics were older, had a higher BMI, and more co-morbidities compared to non-users. Moreover, antidepressant users more often used insulin (27.2% vs. 21.5%). Finally, glycaemic control did not differ between users and non-users (51-52 mmol/mol vs. 52 mmol/mol).

In the last part of this thesis, we described two interventions to improve patient involvement in their T2DM treatment and evaluate treatment strategies(chapter 7,8).

The study described in **chapter 7** evaluated the feasibility of a web-based guided insulin self-titration program in people with T2DM. The most important lesson to be learned was to investigate the potential barriers that PCPs may face before implementing an e-health program in order to a) try to embed and tailor a program to the PCP organisation b) decide on not to implement if doubts exist about embedding or need is lacking. Other option is to change the setting of implementation towards a setting facilitating embedding or towards a setting with an existing need for e-health application.

The study described in **chapter 8** described the development of a tool for clinical medication review to facilitate and support the periodic review of (older) patients' medication by community pharmacists and primary care physicians. A structured, comprehensive and practical tool to assist pharmacists and general practitioners to perform clinical medication review including a list of potential drug-related problems in older patients with chronic disease, as well as a script for structured patient interviews, was developed.

Chapter 9 provides a general discussion based on main findings and future perspectives.

Nederlandse Samenvatting



NEDERLANDSE SAMENVATTING

Diabetes Mellitus Type 2 (T2DM) is een chronische ziekte die zich kenmerkt door hoge bloedglucose waarden (HbA1c levels). De klachten bij T2DM ontstaan vaak heel geleidelijk. Door de verhoogde bloedglucose waarden hebben mensen met T2DM een verhoogd risico op de ontwikkeling van micro en macro vasculaire complicaties.

In de algemene introductie van dit proefschrift worden de huidige behandeldoelen en behandelstrategieën in T2DM besproken. Het doel van dit proefschrift is meer inzicht te krijgen in de huidige behandeldoelen en de effectiviteit van behandelstrategieën op de glucose regulatie bij mensen met T2DM in de dagelijkse praktijk. Eveneens is gekeken naar de evaluatie van een interventie om mensen met T2DM meer te betrekken bij hun behandeling. Tot slot is de ontwikkeling van een interventie om de diabetes behandeling te optimaliseren beschreven.

Het eerste deel van het proefschrift (hoofdstuk 2-4) is toegespitst op de behandeling van T2DM in de praktijk, waarbij in hoofdstuk 2 de resultaten getoond worden van de tijd tot start van insuline bij mensen met T2DM welke niet goed ingesteld zijn op orale bloedglucose verlagende middelen. De lange termijn uitkomsten, zoals glycemische controle, micro vasculaire complicaties en mortaliteit zijn onderzocht. Deze studie laat zien dat 2/3 van de mensen met T2DM insuline gaat gebruiken gedurende de looptijd van deze studie. De tijd tot start van insuline varieerde van 1.2 jaar (range 0.3-3.1) in mensen met HbA1c levels continu ≥ 53 mmol/mol (7.0%) tot 5.4 jaar (range 3.0-7.5) in mensen met fluctuerende HbA1c levels rond de 53 mmol/mol (7.0%). Langere diabetes duur (HR 1.04 95% BI 1.03-1.05) en lagere leeftijd (HR 1.00 95% BI 0.99-1.00) op baseline zijn geassocieerd met een snellere start van insuline. De mensen die gestart zijn met insuline gedurende dit onderzoek hadden meer retinopathie in vergelijking tot mensen die op orale bloedglucose verlagende middelen bleven.

Met behulp van latente klasse analyse, een innovatieve statistische methode, zijn vier subgroepen in insulinegebruikers geïdentificeerd die ieder, na de start van insuline, een verschillend verloop in glucoseregulatie laten zien (hoofdstuk 3). De grootste subgroep (88.7%) laat een stabiele glucoseregulatie zien met HbA1C levels rond de 57 mmol/mol. Slechts 24.4% van de mensen met T2DM bereikten het doel van HbA1c levels onder de 53 mmol/mol. Deze mensen waren 'on-target'. Het behalen van dit doel was geassocieerd met een lager HbA1c level en een hogere leeftijd op het moment van start van insuline.

In hoofdstuk 4 zijn in de totale T2DM populatie vier subgroepen onderscheiden die ieder een verschillende glucoseregulatie over de tijd laten zien: een goede glucoseregulatie groep, een snelle responders groep, een matige glucoseregulatie groep en een non-responders groep. Meer dan 90% van de mensen had goed gecontroleerde en stabiele HbA1c waardes gedurende de

onderzoekperiode. Hogere HbA1c waarden, een langere diabetesduur en een lagere leeftijd bij diagnose waren geassocieerd met een minder gunstig verloop van de glucoseregulatie.

Het tweede deel van dit proefschrift focust zich op co-morbiditeiten in de behandeling van T2DM (hoofdstuk 5 en 6).

Vier subgroepen met een verschillende bloeddrukregulatie zijn in de T2DM populatie geïdentificeerd met behulp van latente klasse analyse (hoofdstuk 5). De grootste subgroep (85.6%) had een adequate bloeddrukregulatie (systolische bloeddruk ≤ 140 mmHg). De tweede subgroep (5.6%) had een verlate respons op antihypertensiva, de derde subgroep (3.4%) had een onvoldoende respons gedurende de eerste vier jaar, en de laatste subgroep (5.6%) vertoonde geen respons op antihypertensiva. Mensen in subgroep 2 t/m 4 waren significant ouder, vaker van het vrouwelijke geslacht en gebruikten meer antihypertensiva. Daarbij hadden deze groepen een hogere prevalentie retinopathie, microalbuminuria en cardiovasculaire mortaliteit.

In hoofdstuk 6 is het gebruik van antidepressiva in personen met T2DM beschreven en zijn de socio-demografische kenmerken van deze mensen onderzocht. Van de 7,016 personen met T2DM, gebruikten 7.1% antidepressiva, 6.5% gebruikten anxiolytica en/ of hypnotica en 3.6% gebruikt een combinatie van antidepressiva, anxiolytica en/ of hypnotica. Gebruikers van deze geneesmiddelen waren vaker van het vrouwelijke geslacht, niet-Kaukasisch en lager opgeleid in vergelijking met niet-gebruikers. Anxiolytica en/ of hypnotica gebruikers waren ouder, hadden een hoger BMI en meer co-morbiditeiten in vergelijking met niet-gebruikers. Antidepressiva gebruikers gebruikten vaker insuline (27.2% vs. 21.5%). De glycemische controle tussen gebruikers van antidepressiva, anxiolytica en hypnotica verschilde niet met niet-gebruikers (51-52 mmol/mol vs. 52 mmol/mol).

In het laatste deel van dit proefschrift zijn twee interventies beschreven om de betrokkenheid van mensen met T2DM in hun diabetes behandeling te vergroten en om behandelstrategieën te evalueren (hoofdstuk 7,8).

De studie die beschreven wordt in hoofdstuk 7 evalueert de haalbaarheid van implementatie van een web-based insuline titratieprogramma ontwikkeld voor mensen die met insuline starten. De belangrijkste les die geleerd kan worden uit deze studie is dat eerst de barrières welke huisartsen hebben ten aanzien van een e-health programma geïnventariseerd worden voordat er gestart wordt met de implementatie. Dit om een programma te ontwikkelen wat beter past in de huidige huisartsenpraktijk en daardoor eenvoudiger en succesvol te implementeren is.

De studie die beschreven wordt in hoofdstuk 8 beschrijft de ontwikkeling van een instrument voor een klinische medicatie review welke gebruikt kan worden door de openbare apotheker en huisarts. Het ontwikkelde instrument bevat een lijst met potentiële medicatie gerelateerde problemen en een script voor een gestructureerd gesprek met de patiënt.

Hoofdstuk 9 biedt een discussie gebaseerd op de belangrijkste bevindingen van dit onderzoek. Op basis van het uitgevoerde onderzoek kunnen de volgende aanbevelingen worden gedaan: implementatie van centraal georganiseerde diabetes zorg, een snellere start van insuline, meer aandacht voor hypoglykemie, en meer aandacht voor jongere mensen met diabetes. Daarbij kan mogelijk de rol van de apotheker in de diabeteszorg vergroot worden, zodat de medicatieveiligheid verhoogd wordt en een meer patiëntgerichte benadering gekozen kan worden. Dit kan mogelijk bijdragen aan een hogere effectiviteit van de behandelingsstrategieën in T2DM.

List of publications



LIST OF PUBLICATIONS

Mast MR, Jansen AP, Walraven I, Rauh SP, Van der Heijden AA, Heine RJ, Elders PJ, Dekker J, Nijpels G, Hugtenburg JG. Time to insulin initiation and long term effects of initiating insulin in people with type 2 diabetes mellitus: the Hoorn Diabetes Care System Cohort Study. *European Journal Of Endocrinology* 2016, 174(5):563-7. doi: 10.1530/EJE-15-1149

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Dankwoord



DANKWOORD

In 2012 las ik in het NRC Handelsblad een artikel met de titel 'Promoveren is een voorrecht'. Het artikel beschreef een proces van vier jaar ongestoord al je concentratie, energie en denkkraft op een vraagstuk loslaten. Na het lezen van dit artikel dacht ik: 'wie wil dat nu niet?'. Terugkijkend op deze vier jaar moet ik concluderen dat de term 'ongestoord', en 'al je energie' niet echt klopt in het geval van parttime promoveren. Toch mag dit de pret niet drukken, en heb ik gedurende het promotietraject enorm veel hoogtepunten maar ook dieptepunten mee mogen maken.

Een belangrijk punt wat mij is opgevallen: promoveren doe je niet alleen! De voltooiing van dit proefschrift heb ik te danken aan de mensen om mij heen waar ik de afgelopen jaren hulp van heb gekregen. Zij hebben mij gesteund, inhoudelijk op weg geholpen, en een berg enthousiasme gegeven en daarmee gezorgd dat ik bleef doorgaan met dit soms wat trage onderzoeksproces.

Alle **deelnemers** van de Hoorn Studie en de **deelnemers** van het Diabetes Zorg Systeem, West-Friesland, zonder jullie deelname aan het onderzoek was het niet mogelijk geweest dit proefschrift te schrijven.

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meermalen langs gekomen, en zeker het vermelden waard: 'Luctor et Emergo', 'Zet hem op, witte muizen!', 'Douw op je kop, en veer op'. En **zie hier** het eindresultaat!

Liefs Ruth

Curriculum Vitae



CURRICULUM VITAE

Maria Ruth Mast werd geboren op 24 December 1983 in Roosendaal en Nispen. Na het afronden van het VWO in 2002 aan het Zeldenrust-Steelant College te Terneuzen, is zij begonnen met haar studie Farmacie aan de Universiteit van Utrecht. De eerste kennismaking met wetenschappelijk onderzoek vond plaats in het vierde jaar van haar studie Farmacie, waarbij een half jaar onderzoek gedaan is aan de McMaster University in Hamilton, Canada. Het betrof een onderzoek naar de fysiologische en pathologische respons van elastase blootstelling in muizen. In het laatste jaar van haar studie heeft ze twee maanden onderzoek gedaan in Ghana naar de mogelijkheden van optimalisatie van voorraadbeheer van geneesmiddelen in verschillende missieziekenhuizen. Gedurende de Masterfase van haar studie is Ruth eveneens werkzaam geweest in Apotheek de Gaard in Utrecht.

In Maart 2009 heeft zij haar Masterdiploma in de Farmacie behaald en is haar loopbaan als apotheker gestart in Service Apotheek Westwijk in Amstelveen. Kort daarop is zij gaan assisteren bij promotieonderzoek naar intensieve begeleiding bij ontslagmedicatie aan het VU Medisch Centrum. In 2012 is ze naast haar baan in Service Apotheek Westwijk begonnen met haar promotieonderzoek bij de afdeling Klinische Farmacologie & Apotheek en de afdeling Huisartsen-geneeskunde & Ouderengeneeskunde onder begeleiding van Prof. G. Nijpels (promotor), Dr. J.G. Hugtenburg, Dr. A.P.D. Janssen en Dr. F. Rutters (copromotors) aan het VU Medische Centrum. Eveneens is zij in 2012 gestart met de opleiding tot Epidemioloog B, welke in 2016 wordt afgerond.

Sinds April 2016 is zij werkzaam bij Pharmalead, een detacheringsbureau voor apothekers.